PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 243/04, 401/04, 401/14, 417/14, 409/14, 413/04, A61K 31/55

A1

(11) International Publication Number: WO 97/38984

(43) International Publication Date: 23 October 1997 (23.10.97)

(21) International Application Number: PCT/US97/06431

(22) International Filing Date: 17 April 1997 (17.04.97)

(30) Priority Data:

60/015,684	17 April 1996 (17.04.96)	US
08/647,127	9 May 1996 (09.05.96)	US
60/042,532	1 April 1997 (01.04.97)	US
08/838,246	16 April 1997 (16.04.97)	US

(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventors: MADUSKUIE, Thomas, Peter, Jr.; 613 Foulkstone Road, Wilmington, DE 19803 (US). GALEMMO, Robert, Anthony, Jr.; 3039 Stump Hall Road, Collegeville, PA 19426 (US). DOMINGUEZ, Celia; 202 Sleepy Hollow Court, Newark, DE 19711 (US). QUAN, Mimi, Lifen; 113 Venus Drive, Newark, DE 19711 (US). ROSSI, Karen, Anita; Apartment D3, 5414 Valley Green Drive, Wilmington, DE 19808 (US). STOUTEN, Petrus, Fredericus, Wilhelmus; 2511 St. George Street, Wilmington, DE 19808 (US). SUN, Jung, Hui; 149 Aintree Lane, Hockessin, DE 19707 (US). WELLS, Brian, Lloyd; 3125 Wilmont Drive, Wilmington, DE 19810 (US).

(74) Agent: VANCE, David, H.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

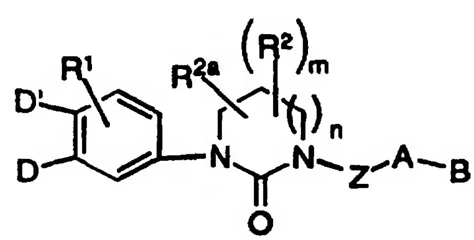
(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: N-(AMIDINOPHENYL)-N'-(SUBST.)-3H-2,4-BENZODIAZEPIN-3-ONE DERIVATIVES AS FACTOR XA INHIBITORS

(57) Abstract

The present application describes N-(amidinophenyl) cycloures analogs of formula (I) which are useful as inhibitors of factor Xa.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece	**ML**	Mali	**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**MN**	Mongolia	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MR**	Mauritania	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MW**	Malawi	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MX**	Mexico	**US**	United States of America
CA	Canada	**IT**	Italy	**NE**	Niger	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NL**	Netherlands	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NO**	Norway	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NZ**	New Zealand	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**PL**	Poland		
CM	Cameroon	**KR**	Republic of Korea	**PT**	Portugal		
CN	China	**KZ**	Kazakstan	**RO**	Romania		
CU	Cuba	**LC**	Saint Lucia	**RU**	Russian Federation		
CZ	Czech Republic	**LI**	Liechtenstein	**SD**	Sudan		
DE	Germany	**LK**	Sri Lanka	**SE**	Sweden		
DK	Denmark	**LR**	Liberia	**SG**	Singapore		
EE	Estonia						

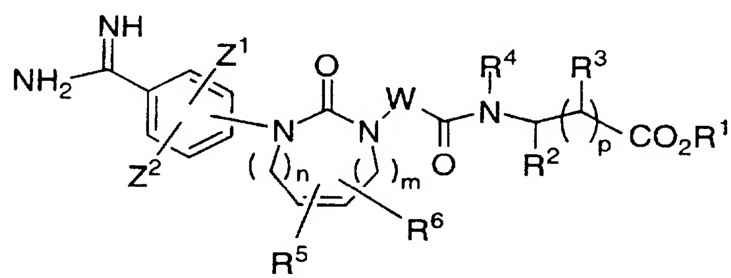
N-(AMIDINOPHENYL)-N'-(SUBST.)-3H-2,4-BENZODIAZEPIN-3-ONE DERIVATIVES AS FACTOR XA INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to N-(amidinophenyl) cycloureа analogs which are inhibitors of factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

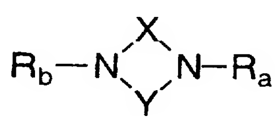
BACKGROUND OF THE INVENTION

Bovy et al, U.S. Patent No. 5,430,043 describe phenyl amidines of the formula:



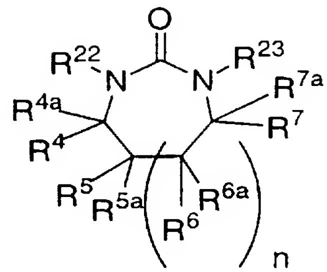
which are reported to be platelet aggregation inhibitors. However, no mention is made of inhibiting Factor Xa.

Himmelsbach et al, CA 2,105,934, address cyclic ureas of the formula:



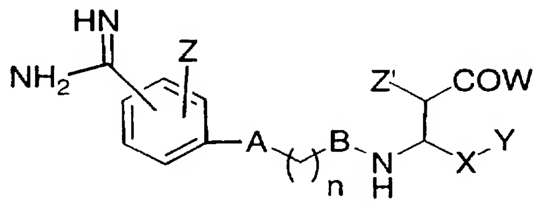
wherein, among the multitude of choices, X may be a carbonyl, Y may be an C_{2-4} alkylene, R_a may be A-B-C- and R_b may be -D-E-F. Group F is selected from $-CO_2R$, phosphono, tetrazolyl, and $R_8CO-O-CHR_9-O-CO-$. The compounds described by the above formula are alleged to have aggregation inhibiting and/or fibrinogen binding properties. Factor Xa inhibiting is not discussed.

Lam et al, WO 94/19329, report cyclic carbonyls which may be cyclic ureas of the formula:



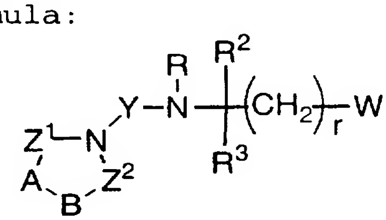
wherein at least one of R^4, R^{4a}, R^7, and R^{7a} is other than hydrogen. Compounds of this sort are said to be useful as HIV protease inhibitors. N-(Amidinophenyl)cycloureas are not suggested as factor Xa inhibitors.

Currie et al, WO 96/36639, set forth amidine derivatives of the formula:



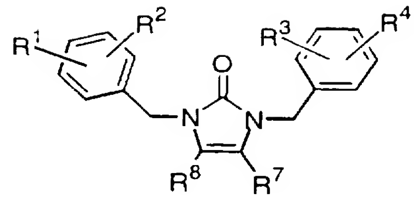
wherein A may be a 6-membered cyclic urea, which may be useful as anti-platelet aggregation inhibitors. However, Y is nitrate, nitrite, or a nitric oxide donating group. The present compounds, in contrast, do not contain the nitric oxide donating groups of WO 96/36639.

Klinger et al, WO 94/21607, illustrate heterocyclic compounds of the formula:



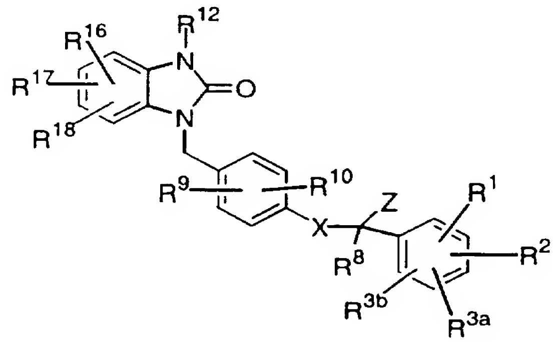
wherein, upon judicious selection of variables, Z^1 may be a carbonyl, A may be NR^1, R^1 may be an amidino-substituted phenyl, and B and Z^2 may each be CH_2. However, the present compounds do not include the right-side chain shown above.

Mohan et al, WO 96/38421, describe N,N-di(arylmethyl)cyclic urea derivatives of the formula:



wherein R^7 and R^8 may combine to form a benzene ring and the double bond shown may be absent, which may be useful as Factor Xa inhibitors. These compounds are preferably bis-amidino substituted. However, the presently claimed compounds are neither bis-benzyl nor bis-amidino substituted.

Chakravarty et al, WO 95/03044, discuss benzimidazoles substituted with phenoxyphenylacetic acid dervatives of the formula:



wherein R^{12} may be a substituted aryl group. But, this reference does not consider amidino-phenyl groups. Furthermore, the present compounds do not contain the above variable Z, which is defined as a carbonyl, sulfonyl, or phosphoryl group.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (*Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of*

the complex in the amplification of blood coagulation. Thromb. Res. 1979, 15, 617-629), inhibition of factor Xa may be more efficient that inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

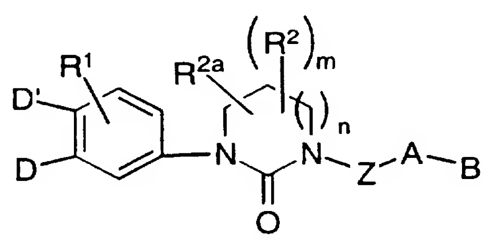
SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel N-(amidinophenyl)cyclourea factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

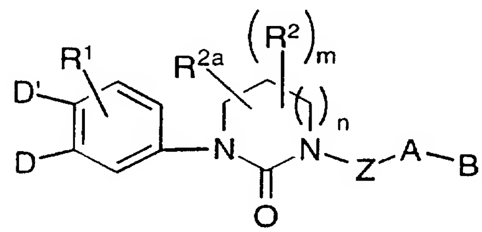


I

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, R^1, R^2, m and n are defined below, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formula I:



I

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein;

one of D and D′ is selected from CN, $C(=NR^{11})NR^{12}R^{13}$, $NHC(=NR^{11})NR^{12}R^{13}$, $NR^{12}CH(=NR^{11})$, $C(O)NR^{12}R^{13}$, and $(CH_2)_tNR^{12}R^{13}$ and the other is H;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, C_{1-4} alkyl, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNR^4SO_2R^5$;

R^2 is selected from H, =O, C_{1-4} alkyl substituted with 0, 1, or 2 R^7, C_{2-6} alkenyl substituted with 0, 1, or 2 R^7, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, C_{3-10} carbocyclic residue substituted with 0-2 R^6; and, 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^{2a} is absent;

alternatively, R^2 and R^{2a} may be present on adjacent carbon atoms and combine to form a benzene ring substituted with 0-2 R^{10} or a 5-6 membered aromatic heterocycle containing 0-2 heteratoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{10a};

R^3 and $R^{3'}$ are independently selected from H, C_{1-4} alkyl, benzyl and phenyl;

R^3 and $R^{3'}$ may be taken together to form a 5 or 6 membered ring substituted with 0-2 R^6;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, phenyl and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl, phenyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_2NR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_2OC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)O(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^6, and

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

B is selected from:

X-Y, $NR^3R^{3'}$, $C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$,

benzyl substituted with 0-2 R^6,

C_{3-10} carbocyclic residue substituted with 0-2 R^6, and

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-C(O)O-$, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, $-OC(O)-$, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-CR^3R^{3'}S(O)_p-$, $-S(O)_2NR^3-$, $-NR^3S(O)_2-$,

$-NR^3S(O)_2CR^3R^{3\prime}-$, $-CR^3R^{3\prime}S(O)_2NR^3-$, $-NR^3S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-C(O)NR^3CR^3R^{3\prime}-$, $-NR^3C(O)CR^3R^{3\prime}-$, $-CR^3R^{3\prime}C(O)NR^3-$, $-CR^3R^{3\prime}NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3\prime}-$, $-CR^3R^{3\prime}NR^3-$, O, $-CR^3R^{3\prime}O-$, $-OCR^3R^{3\prime}-$, S, $-CR^3R^{3\prime}S-$, and $-SCR^3R^{3\prime}-$;

Y is selected from:

C_{1-4} alkyl substituted with 0-2 R^6

C_{3-10} carbocyclic residue substituted with 0-2 R^6, and

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, $NR^3SO_2-C_{1-4}$ alkyl, SO_2-phenyl, and $NR^3SO_2R^8$;

R^7 is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^6; and,

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^8 is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^9; and,

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^9;

R^9 is selected from H, OH, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, and $NR^3SO_2-C_{1-4}$ alkyl;

R^{10} is selected from H, OR^3, halo, C_{1-4} alkyl, CN, NO_2, $NR^3R^{3\prime}$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)OR^{3\prime}$, NR^3SO_2-phenyl, and $NR^3SO_2-C_{1-4}$ alkyl;

R^{10a} if a substituent on nitrogen is selected from H and C_{1-4} alkyl;

R^{10a} if a substituent on carbon is selected from H, C_{1-4} alkyl, $NR^3R^{3'}$, $NR^3C(O)R^{3'}$, $NR^3C(O)OR^{3'}$, NR^3SO_2-phenyl, and NR^3SO_2-C_{1-4} alkyl;

R^{11} is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^{12} is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

R^{13} is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

n is selected from 0, 1, 2, and 3;

m is selected from 0 and 1;

p is selected from 0, 1, and 2;

q is selected from 1, 2, 3, 4, and 5; and,

r is selected from 0, 1, and 2.

[2] In a preferred embodiment, the present invention provides compounds of formula I wherein:

D is $C(=NH)NH_2$;

D' is H;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNHSO_2R^5$;

R^2 is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, C_{3-10} carbocyclic residue substituted with 0-2 R^6; and, 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$; and,

X is selected from C_{1-4} alkylene, -C(O)-, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, -C(O)O-, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, -OC(O)-, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-CR^3R^{3'}S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3'}-$, $-CR^3R^{3'}NR^3-$, O, $-CR^3R^{3'}O-$, and $-OCR^3R^{3'}-$.

[3] In a more preferred embodiment, the present invention provides compounds of formula I wherein:

R^1 is selected from H, OR^3, $(CH_2)OR^3$, halo, $NR^4R^{4'}$, $(CH_2)NR^4R^{4'}$, $C(=O)R^4$, $(CH_2)C(=O)R^4$, $NHC(=O)R^4$, $(CH_2)NHC(=O)R^4$, SO_2R^5, $(CH_2)SO_2R^5$, $NHSO_2R^5$, and $(CH_2)NHSO_2R^5$;

R^2 is selected from H, =O, OR^3, $C(O)R^4$, $(CH_2)C(O)R^4$, $OC(O)R^4$, $NR^4R^{4'}$, $NR^3C(O)R^4$, and $NR^4SO_2R^5$;

A is selected from:

C_{5-6} carbocyclic residue substituted with 0-1 R^6, and

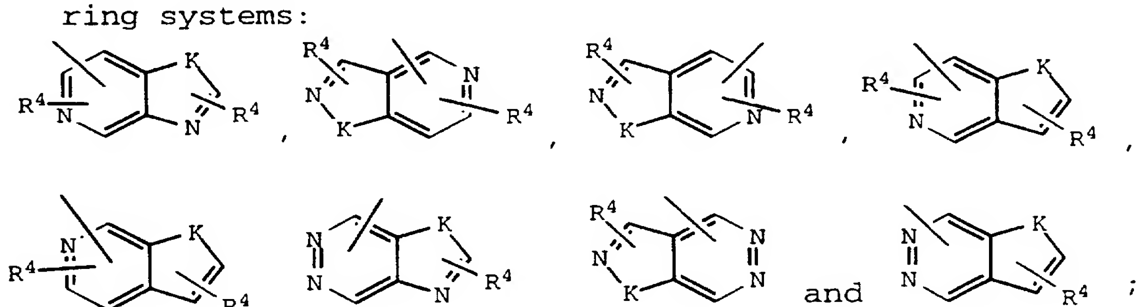
5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N and O substituted with 0-1 R^6;

B is selected from: Y, X-Y, and NR^2R^{2a};

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, isoindazole, and benzothiadiazole;

Y may also be selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N;

X is selected from $-CH_2-$, $-C(O)-$, $-C(O)CHR^3-$, $-CHR^3C(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3\prime}-$, $-CHR^3S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3-$, $-NR^3CHR^3-$, and $-CHR^3NR^3$;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $SO_2NR^3R^{3\prime}$, SO_2-phenyl, NR^3SO_2-C_{1-4} alkyl, and $NR^3SO_2R^8$;

R^8 is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^9; and,

5-6 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^9;

R^9 is selected from H, OH, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, and NR^3SO_2-C_{1-4} alkyl; and,

p is 2.

[4] In an even more preferred embodiment, the present invention provides compounds of formula I wherein:

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, and $(CH_2)_rS(CH_2)_r$;

X is selected from $-CH_2-$, $-C(O)-$, $-C(O)CHR^3-$, $-CHR^3C(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3\prime}-$, $-CHR^3S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, and $-NR^3C(O)-$;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $SO_2NR^3R^{3\prime}$, SO_2-phenyl, and NR^3SO_2-C_{1-4} alkyl;

m is 1; and,

r is selected from 0 and 1.

[5] In a further preferred embodiment, the present invention provides compounds of formula I wherein:

R^3 and $R^{3'}$ are independently selected from H and C_{1-4} alkyl;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, and $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$;

A is selected from phenyl substituted with 0-1 R^6 and a 6 membered heterocyclic system containing 1 N and 0-1 O atoms and substituted with 0-1 R^6;

X is selected from $-CH_2-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, and ;

Y is selected from phenyl, i-propyl, quinolynyl, thiadizolyl, benzothiadiazolyl, thiophenyl, pyridyl, cyclohexyl, and naphthyl, each of which is substituted with 0-2 R^6; and,

n is selected from 0, 1, and 2.

[6] In an even further preferred embodiment, the present invention provides compounds of formula I wherein:

R^3 and $R^{3'}$ are independently selected from H and methyl;

Z is selected from a bond, CH_2, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-$;

A is selected from phenyl substituted with 0-1 R^6, and piperidinyl substituted with 0-1 R^6; and,

n is 2.

[7] In a particularly preferred embodiment, the present invention provides compounds selected from:

N-(3-amidinophenyl)-N'-((4-((2-sulphonamido)phenyl)phenyl)-methyl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-2-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-3-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-4-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(a-phenethyl)piperidin-4-yl)cyclo-heptylurea;

N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperi-din-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(phenyl)sulfonylpiperidin-4-yl)-cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(quinolin-8-yl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-fluorophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-acetamidophenyl)sulfonyl-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(3-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-acetamido-phenyl)methane)-sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((thiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-chlorothiophen-2-yl)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-carbomethoxythiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((benzo-2,1,3-thiadiazo-4-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((cyclohexyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((isopropyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((phenyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((isopropyl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-amino-4-methylthiazol-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-acetamido-4-methylthiazol-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(6-carbomethoxyphenyl-sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(3-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(phenyl-N''-methylsulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((4-phenylsulfonylthiophen-2-yl)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-pyridylmethylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(thiophen-2-ylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-fluorobenzylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-pyridylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-trifluormethyl-phenylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-phenylisopropylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)carbamide)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((thiophen-2-yl)sulfonyl)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)sulfonyl)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-(benzyl)sulfonyl)-piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-(thiophen-2-yl)sulfonyl)piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-(2-sulfonamido-phenyl)phenyl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(5-(2-sulfonamido-phenyl)pyridin-2-yl)cycloheptylurea; and,

N-(3-amidinophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)phenyl))cycloheptylurea;

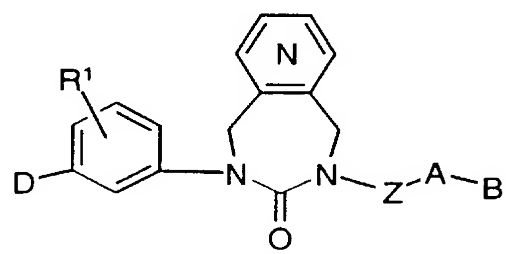
or stereoisomers or pharmaceutically acceptable salt forms thereof.

[8] In another preferred embodiment, the present invention provides compounds wherein:

n is 2; and,

R^2 and R^{2a} are on adjacent carbon atoms and combine to form a benzene ring substituted with 0-2 R^{10} or a 5-6 membered aromatic heterocycle containing 0-2 heteratoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{10a}.

[9] In another more preferred embodiment, the present invention provides novel compounds of formula II:



II

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein;

ring N contains 0-2 N atoms and is substituted with 0-2 R^{10}; and,

D is selected from CN, $C(=NR^{11})NR^{12}R^{13}$, $NHC(=NR^{11})NR^{12}R^{13}$, $NR^{12}CH(=NR^{11})$, $C(O)NR^{12}R^{13}$, and $(CH_2)_tNR^{12}R^{13}$.

[10] In another even more preferred embodiment, the present invention provides compounds of formula II wherein:

D is $C(=NH)NH_2$;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNHSO_2R^5$;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, and $(CH_2)_rSO_2NR^3(CH_2)_r$; and,

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-C(O)O-$, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, $-OC(O)-$, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-CR^3R^{3'}S(O)_p-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3'}-$, $-CR^3R^{3'}NR^3-$, O, $-CR^3R^{3'}O-$, and $-OCR^3R^{3'}-$.

[11] In another further preferred embodiment, the present invention provides compounds of formula II, wherein:

Z is selected from a bond, C_{1-4} alkylene, $C(O)NR^3(CH_2)_r$, $S(O)_2$, $S(O)_2CH_2$, and $(CH_2)_rSO_2NR^3(CH_2)_r$;

A is selected from phenyl substituted with 0-1 R^6 and 6 membered heterocyclic system containing 1 N and substituted with 0-1 R^6; and,

X is selected from C_{1-4} alkylene, -C(O)-, -C(O)$CR^3R^{3'}$-, -$CR^3R^{3'}$C(O)-, -$S(O)_p$-, -$S(O)_pCR^3R^{3'}$-, -C(O)NR^3-, and, -NR^3-.

[12] In another even further preferred embodiment, the present invention provides compounds selected from:

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one;

1,2,4,5-tetrahydro-2-(thiopen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one;

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one; and,

1,2,4,5-tetrahydro-2-(thiophen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one.

In a second embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug form thereof.

In a third embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug form thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the atom of the compound of a given formula, then such substituent may be bonded via any atom in such

substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C_{1-6} alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which

results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, benzothiadiazolyl, carbazolyl, 4a*H*-carbazolyl, β-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl,

pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic,

lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amidine prodrugs wherein D is $C(=NR^{11})NH_2$, and R^{11} is selected from OH, C_{1-4} alkoxy, C_{6-10} aryloxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, and C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl. More preferred

prodrugs are where R^{11} is OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

Compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Each of the references cited below are hereby incorporated herein by reference. All the temperatures are reported herein in degrees Celsius.

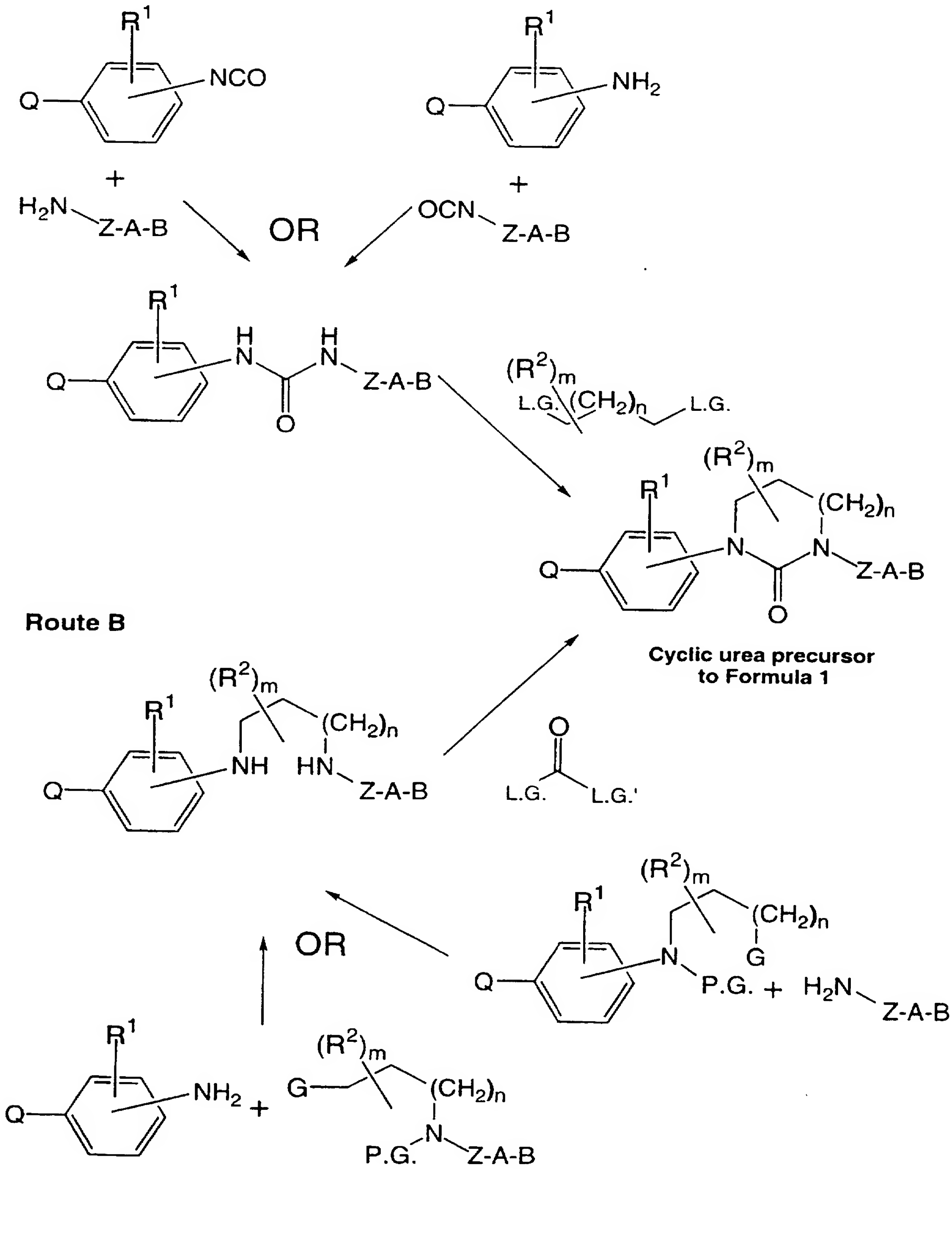
The compounds of Formula 1 can be prepared using the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the

trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, **1991**).

Two general approaches can be used for the preparation of the cyclic ureas of this invention. The first involves bimolecular cyclizations to the cyclic urea, as outlined in Scheme I, the second uses the internal unimolecular cyclizations of Scheme II.

Scheme I: Bimolecular cyclization routes to a cyclic urea precursor to Formula 1.

Route A



Route A of Scheme I illustrates the bis-alkylation of an N,N'-disubstituted urea with an alkane substituted at both termini with an appropriate leaving group (L.G.), such as a halogen or sulfonate ester. The flexibility of this approach also allows for the bis-alkylation with an alkene or R^2-substituted alkane which is again substituted at both termini with an appropriate leaving group (L.G.). Such alkylation agents are either commercially available, e.g. 1,4-dibromobutane and its lower homologs, found in the literature, e.g. the isopropylidene ether of 1,4-diiodido-2,3-dihydroxybutane (Deluca and Magnus, *J. Chem. Soc.* (Perkin Trans. I), 2661(1991), and Hoye and Suhadolnik, *Tetrahedron*, **42** (11) 2855 (1986)), or can be prepared by a practitioner skilled in the art using standard chemical methods.

The N,N'-disubstituted urea can be generated from two primary amines, one of which must be a Q,R^1-substituted aniline wherein Q is a functional group from which an amidine could be readily generated such as nitrile; in some special cases Q may be tolerated as a mono- or di- acyl or carbamoyl protected amidine. The second primary amine, H_2N-Z-A-B, may be any amine deemed appropriate within the limits of Formula 1. This amine may be commercially available, e.g. 1-benzyl-4-aminopiperidine, found in the literature, e.g. 1-t-butoxycabonyl-4-aminopiperidine (Mach et al., *J. Med. Chem.*, **36**(23), 3707 (1993)), or can be prepared by a practitioner skilled in the art utilizing standard chemical methods.

The two primary amines described above can be assembled to the desired N,N'-disubstituted urea by selecting one for transformation to the corresponding isocyanate *in situ* by stirring with phosgene or its equivalent such as trichloromethyl chloroformate or p-nitrophenylchloroformate in the presence of a trialkylamine base and a dry, aprotic solvent such as dimethylformamide, dioxane, benzene or a chlorinated alkane. The temperature of this reaction may be varied from -10°C to the reflux point of the solvent (Takeda et al., *Tetrahedron Lett.*, **24**(42) 4569 (1983), Cortez et al., *Synth. Commun.*, **21**(2) 285 (1991)). Alternatively the desired isocyanate may be commercially available, such as

3-cyanophenyl isocyanate, in which case convenience dictates that this substrate be used. Conditions for direct reaction of a preformed isocyanate are similar to those described above with the caveat that the phosgene equivalent is necessary, and the trialkylamine base may be omitted (Shiau et al., *J. Heterocyclic Chem.*, **26**, 595(1989)).

Ring formation in Route A is achieved by alkylation of the N,N'-disubstituted urea with the dihalogenated (Curtis, *Aust. J. Chem.*, **41** 585 (1988), Htay et al., *Tetrahedron Lett.*, 79 (1976), Sulsky et al., *Synth. Commun.*, **19**, 1871 (1989)) or disulfonated (Ayyana et al., *Chem. Ind.* (London), 599 (1988)) alkylating agent described above. Typically, the disubstituted urea is added at ambient temperature or lower to a mixture of at least two equivalents of strong base such as sodium hydride, potassium t-butoxide or an alkyl lithium in an appropriate anhydrous solvent such as tetrahydrofuran, dimethylformamide, t-butanol, toluene or dimethylsulfoxide. After deprotonation is complete, a solution of the alkylating agent in the selected solvent is added slowly to the disubstituted urea at ambient temperature or lower; when the addition is completed, the reaction may be continued at ambient temperature or lower or heated up to the reflux temperature of the solvent, depending upon the reactivity of the alkylating agent/disubstituted urea pair and the patience of the practitioner.

Route B of Scheme I illustrates use of an appropriately substituted diamine and phosgene or its equivalent to generate a cyclic urea precursor to Formula 1. The required diamine can be generated by two approaches. The first approach utilizes a Q,R^1-substituted aniline which is conjoined with an N-acyl or N-carbamoyl protected secondary amine where G is a halogen or sulfonate ester leaving group for a standard alkylation of the Q,R^1-substituted aniline or G could be an aldehyde suitable for reductive alkylation of the Q,R^1-substituted aniline. The second approach to diamine formation conjoins an N-acyl or N-carbamoyl protected N-alkylated Q,R^1-substituted aniline, where G is as described above, with primary amine H_2N-Z-A-B by a standard or reductive alkylation.

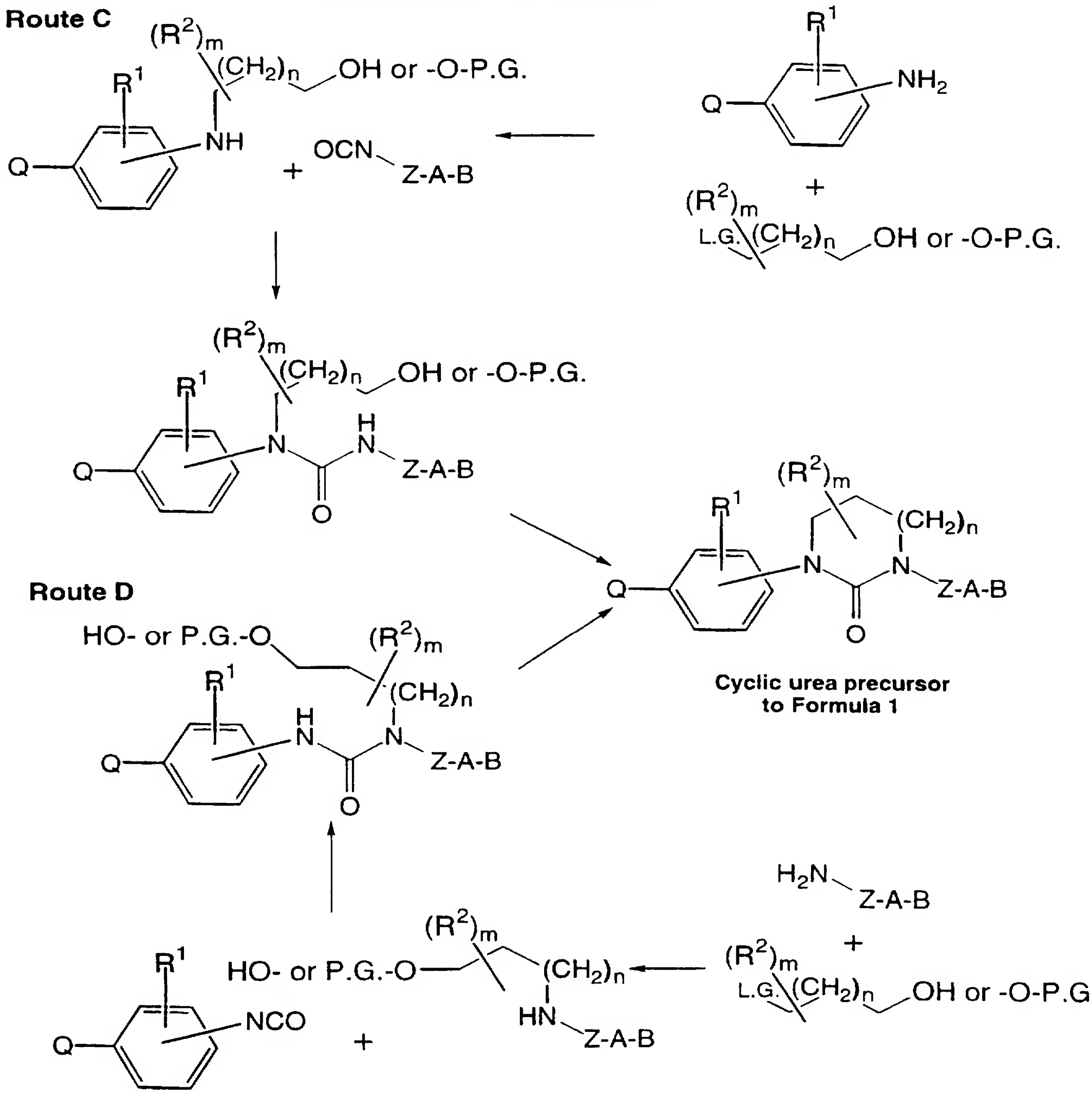
Both protected secondary amines are available by similar chemistry. The selected aniline or primary amine H_2N-Z-A-B is protected with a N-acyl or N-carbamoyl protecting group according to a method specified in Greene and Wuts; N-t-butoxy carbamoyl is useful for this application. This protected amine can then be cleanly mono-alkylated with one of the dihalogenated or disulfonylated alkylating agents recommended for Route A (Reed et al., *Tetrahedron Lett.*, **79**(45) 5725 (1988)). Alternatively, the protected amine can be mono-alkylated with a protected halo alcohol. Both alkylations are readily achieved in anhydrous aprotic solvents such as toluene, tetrahydrofuran, dimethylformamide or dimethylsulfoxide at temperatures ranging from -78°C to the reflux temperature of the selected solvent with a strong base such as sodium hydride, potassium t-butoxide or an alkyl lithium. In the case where G is a protected alcohol, the protecting group is removed and an aldehyde generated by Moffatt oxidation (Pfitzner and Moffatt, *J. Amer. Chem. Soc.*, **87** 5661 (1965)) or through use of pyridinium chlorochromate (Corey and Suggs, *Tetrahedron Lett.*, 2647 (1975)) or pyridinium dichromate in dichloromethane (Coates and Corrigan, *Chem. Ind.* (London), 1594 (1969)).

The required diamine can then be prepared by stirring the alkylating agent with the primary amine component either neat or in an aprotic solvent such as toluene, tetrahydrofuran, dimethylformamide or dimethylsulfoxide. The temperature of this reaction may range from -78°C to the reflux temperature of the selected solvent. A strong base such as sodium hydride, potassium t-butoxide or an alkyl lithium or a weaker trialkylamine base may be used, depending upon the reactivity of the two components. As an alternative, when G is an aldehyde, a reductive alkylation of the primary amine component is possible. The direct method involves the use of a borohydride reducing agent, most preferably sodium or lithium cyanoborohydride, in a mixture of aldehyde and amine components in an alcoholic solvent (Borch et al., *J. Amer. Chem. Soc.*, **93** 2897 (1971)). A stepwise method involves generation of an intermediate imine/enamine by azeotropic

removal of water from a heated mixture of aldehyde and primary amine component in a suitable solvent such as benzene at reflux temperature. The imine/enamine intermediate can then be isolated and reduced by palladium catalyst under an atmosphere of hydrogen gas at ambient pressure or higher or reduced by borohydride reagents under conditions similar to those preferred for the direct method. The required diamine is generated by removal of the protecting group according to a method recommended in Greene and Wuts.

The diamine formed above is reacted with phosgene or its equivalent such as trichloromethyl chloroformate or p-nitrophenylchloroformate in the presence of an excess of a trialkylamine base and a dry, aprotic solvent such as dimethylformamide, dioxane, toluene, benzene or a chlorinated alkane to form a cyclic urea precursor to Formula 1. The temperature of this reaction may be varied from -10°C to the reflux point of the solvent.

Scheme II: Unimolecular cyclization routes to cyclic urea precursors to Formula 1.



Two alternatives, Route C and Route D, for the preparation of precursors of Formula 1 by a unimolecular cyclization method are outlined in Scheme II. In Route C one begins by alkylating a Q,R^1-substituted aniline with a halogenated alkylalcohol, such as 4-bromobutan-1-ol or its

homologs, or a protected version of the same, such as the methoxymethyl ether of 4-bromobutan-1-ol, either neat or in an anhydrous solvent such as dimethylformamide, benzene, tetrahydrofuran, hexamethylphosphorotriamide, or dimethylsulfoxide. This reaction may be furthered by heating the mixture up to the reflux point of the solvent. Depending upon the reactivity of the substrate no base, or a strong base, such as sodium hydride, potassium t-butoxide or an alkyl lithium, or a weak base, such as potassium carbonate or a trialkylamine, may be necessary. The alkylation product is then reacted with an isocyanate OCN-Z-A-B generated from the amine NH_2-Z-A-B by the same method described above for Route A of Scheme I to give a product alcohol or protected alcohol which can be transformed to a halogenated or sulfonyl ester analog for cyclization to a cyclic urea precursor to Formula 1.

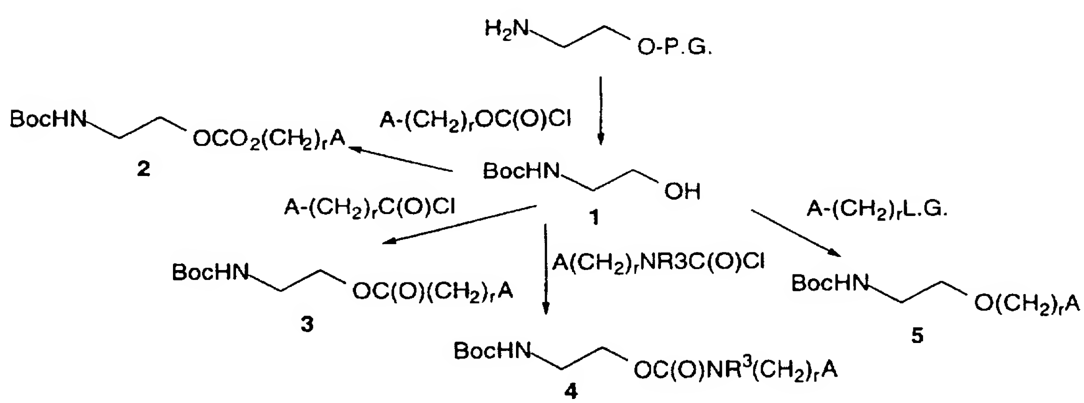
Following deprotection according to an appropriate method found in Greene and Wuts (if necessary), halogenation of the primary alcohol can be carried out with a variety of reagents such as neat thionyl chloride, triphenylphosphine in carbon tetrachloride (Lee and Downie, *Tetrahedron*, **23** 359 (1967)), or triphenylphosphine with N-chloro- or N-bromosuccinimide in dimethylformamide. The alternative sulfonyl ester is also readily prepared from an appropriate sulfonyl chloride, such as the commercially available p-toluenesulfonyl chloride or methanesulfonyl chloride, in a variety of anhydrous aprotic solvents, such as pyridine, benzene, tetrahydrofuran or a chlorinated hydrocarbon, with or without cooling, and with or without a trialkylamine base.

Ring closure to a cyclic urea precursor to Formula 1 has been observed to occur spontaneously in some cases, but may be furthered in an anhydrous solvent such as dimethylformamide, benzene, tetrahydrofuran, hexamethylphosphorotriamide, or dimethylsulfoxide, by heating the mixture up to the reflux point of the solvent. Depending upon the reactivity of the substrate no base, or a strong base, such as sodium hydride, potassium t-butoxide or an alkyl lithium, or a weak base, such as potassium carbonate or a trialkylamine, may be necessary.

Route D of Scheme II may be advantageous over Route C for the availability of starting materials such as the commercially produced 1-benzyl-4-aminopiperidine for NH_2-Z-A-B component, 2-bromoethanol for the halo alcohol component, and 3-cyanophenyl isocyanate for the isocyanate component. In any respect, the chemistry described in Route C is applicable to an analogous reaction in Route D with modifications appropriate for the particular materials involved.

In Formula 1 the radical Z serves as a linking group interposed between the cyclic urea structure and radical A-B. For the purposes of this discussion it is recognized that there are variations of Z, that is where Z = a bond or C_{1-4} alkylene or a portion of the defined linkage , that for synthetic purposes are best incorporated as a substituent of A. It is also assumed for the purpose of this discussion that the analog of A used throughout may contain an orthogonal protecting group, which is compatible with the chemistry suggested. Furthermore, this protecting group may be removed to reveal a substituent that can be used to generate a group X.

<u>Scheme III:</u> Preparation of H_2N-Z-A, where Z = $-CH_2CH_2-O-$ functional group.



The preparation of Z outlined in Scheme III begins with the O-protected derivative of 2-aminoethanol. The t-butyldimethylsilyl analog is recommended for this purpose and is know in the literature (see WO 9504277 and WO 9205186).

However, a worker skilled in the art would recognize that the approaches discussed herein are not limited to this particular analog of 2-aminoethanol. O-Protected 2-aminoethanol can then be protected as the N-t-butoxycarbonyl analog and selectively O-deprotected according to procedures found in Greene and Wuts. The resulting 2-(N-t-butoxycarbamoyl)ethanol (**1**) can then be reacted with various analogs of A to give the desired group Z.

Product **2** is the result of reaction of the chlorocarbonate analog of A with **1** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78° to ambient temperature. The carbonyl chloride analog of A ($A(CH_2)_rOC(O)Cl$) is avaialable by reaction of an appropriate alcohol analog of A with phosgene or one of its equivilents in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78° to ambient temperature.

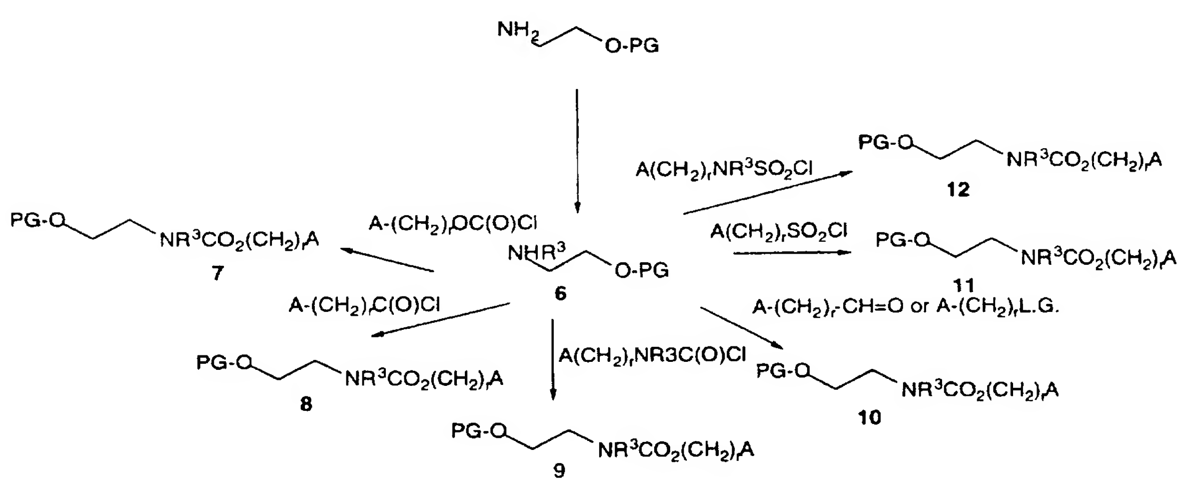
Product **3** is prepared by reaction of the acid chloride of an appropriate acid analog of A with **1** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78° to ambient temperature. The acid chloride can be obtained by reaction of the acid analog of A with phosphorous oxychloride, phosphorous pentachloride, thionyl chloride or oxalyl chloride with or without a non-polar aprotic solvent such as a chlorocarbon, benzene or toluene at temperatures ranging from 0°C to the reflux point of the solvent or neat reagent.

Product **4** can be prepared by the reaction of a carbamoyl chloride analog of A with **1** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78°C to ambient temperature. The carbamoyl chloride analog of A ($A(CH_2)_rNR^3C(O)Cl$) is avaialable by reaction of an appropriate amine analog of A with phosgene or one of its equivilents in a variety of aprotic solvents, such as a

chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78°C to ambient temperature.

Product **5** is available by the reaction of an analog of A substituted with an appropriate leaving group with the alkoxide generated from **2** by treatment of **2** with a stong base such as sodium or potassium hydride or a thallium alkoxide in an aprotic solvent such as dimethylformamide, tetrahydrofuran or dimethylsulfoxide at a temperature ranging from 0 to 120°C. The leaving group of A is most conviently generated from an appropriate alcohol analog of A. The alcohol function can be used to prepare a sulfonate ester from a sulfonyl chloride in a cholorocarbon solvent with a trialkylamine base or in pyridine; alternatively the halogen can be generated from a variety of reagents, triphenyl phosphine and carbon tetrabromide, phosphorous pentabromide or chloride, and thionyl chloride, to name a few.

<u>Scheme IV:</u> Preparation of H_2N-Z-A, where Z = -CH_2CH_2-NR^3- functional group.



The series of analogs in Scheme IV can be prepared from the protected amino alcohol **6** to give products **7** to **12** by methods similar to some of those described for Scheme III. Compound **6** is prepared from 2-amino-(O-t-butyldimethyl-silyl)ethanol by reductive amination of the primary amine by a variety of methods. The primary amine may be reacted with an

aldehyde or ketone under dehydrating conditions to form an imine or enamine intermediate which is then reduced to the N-alkyl derivative using palladium catalyst under an atmosphere of hydrogen in an appropriate solvent. Alternatively, reductive alkylation can be effected by a mixture of the ketone or aldehyde and the amine with lithium or sodium cyanoborohydride in methanol or ethanol as solvent.

It is to be understood that products **7** to **12** need to have the terminal protected oxygen transformed to the primary amine either at this stage or after elaboration with group B. This can conveniently be achieved by deprotection of the primary alcohol. The alcohol function can then be used to prepare a sulfonate ester from a sulfonyl chloride in a chlorocarbon solvent with a trialkylamine base or in pyridine; alternatively a halogen can be generated from a variety of reagents, triphenyl phosphine and carbon tetrabromide, phosphorous pentabromide or chloride, and thionyl chloride, to name a few. The resulting leaving group is then displaced with a mixture of sodium azide in dimethylformamide at an elevated temperature to form the primary azide. The azide can then be reduced to the amine by catalytic hydrogenation in an alcoholic solvent with palladium catalyst under an atmosphere of hydrogen gas at pressures ranging from ambient to 65 psi; an alternative method for effecting this transformation involves refluxing the azide intermediate with triphenylphosphine in benzene or toluene and hydrolyzing the resulting intermediate with aqueous acid.

Product **7** of Scheme IV is the result of the reaction of the chlorocarbonate analog of A with **6** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78°C to ambient temperature. Product **8** is prepared by the reaction of the acid chloride of an appropriate acid analog of A with **6** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78°C to ambient temperature. Product **9** can be prepared by the reaction of a carbamoyl chloride analog of A

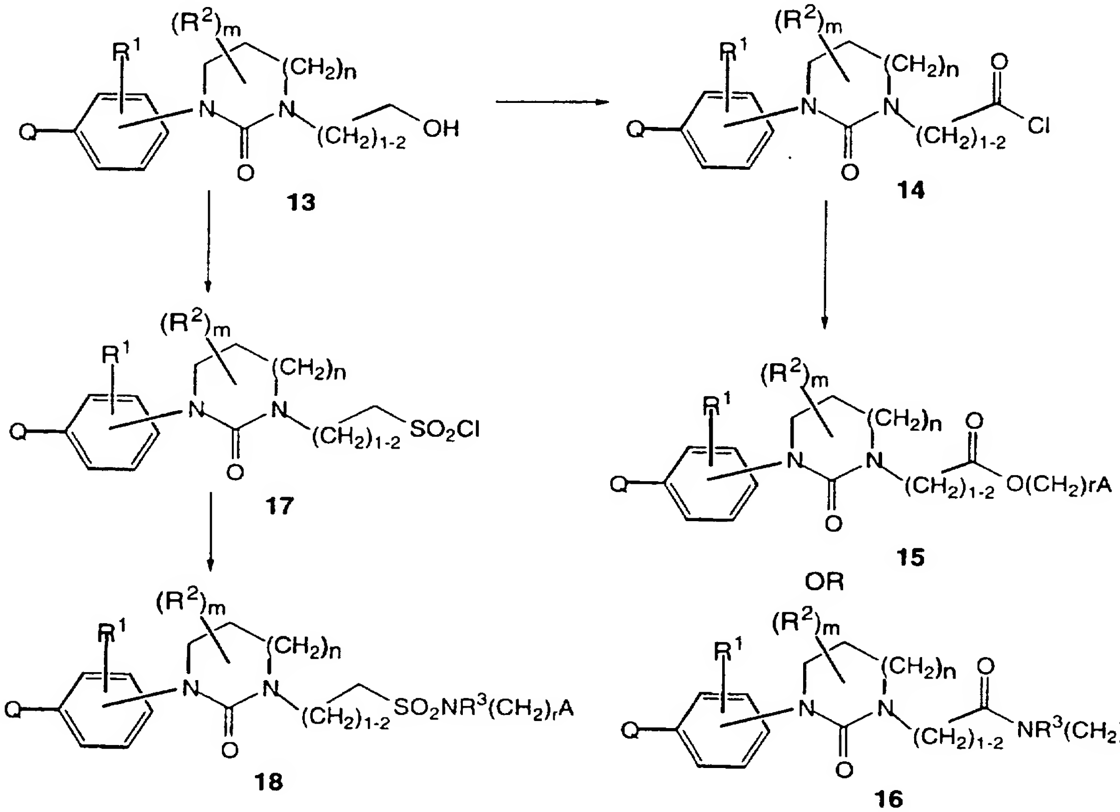
with **6** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78° to ambient temperature.

Product **10** may be obtained from **7** by two routes, conventional alkylation or reductive alkylation. If **6** is a primary amine, then reductive alkylation is recommended. The primary amine **6** may be reacted with an aldehyde or ketone analog of A under dehydrating conditions to form an imine or enamine intermediate which is then reduced to the N-alkyl derivative using palladium catalyst under an atmosphere of hydrogen in an appropriate solvent. Alternatively, reductive alkylation can be effected by a mixture of the ketone or aldehyde and the amine with lithium or sodium cyanoborohydride in methanol or ethanol as solvent. The aldehyde or ketone analog of A is readily accessible from the appropriate alcohol by Swern, Moffat or Jones oxidation. In the case where **6** is a secondary amine product **10** is available by the reaction of an analog of A substituted with an appropriate leaving group with **7** in the presence of a weak base such as a trialkylamine or solid sodium or potassium carbonate in an aprotic solvent such as dimethylformamide, acetone, tetrahydrofuran or dimethylsulfoxide at a temperature ranging from 0° to 120°C.

Product **11** is prepared by the reaction of the sulfonyl chloride of an appropriate analog of A with **6** in a variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78° to ambient temperature. The sulfonyl chloride analog of A is available via the sulfonic acid of A which can be prepared by heating a halogen analog of A in a aqueous sodium sulfite. The sulfonyl chloride of A can be prepared by reacting the sulfonic acid with phosphorous oxychloride, phosphorous pentachloride, thionyl chloride or oxalyl chloride with or without a non-polar aprotic solvent such as a chlorocarbon, benzene or toluene at temperatures ranging from 0°C to the reflux point of the solvent or neat reagent. Product **12** is prepared by the reaction of the sulfamoyl chloride of an appropriate analog of A with **6** in a

variety of aprotic solvents, such as a chlorocarbon, tetrahydrofuran, or pyridine, with or without a trialkylamine base at temperatures ranging from -78°C to ambient temperature.

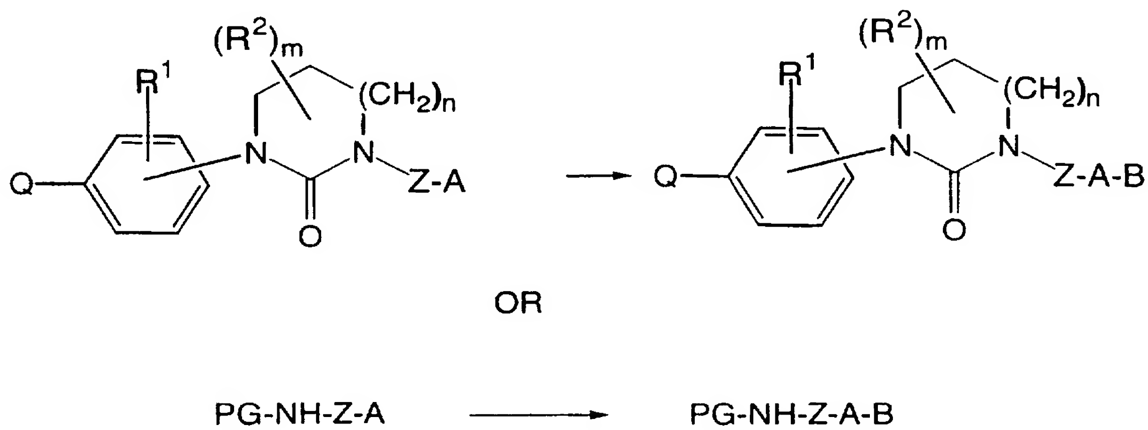
Scheme V: Preparation of compounds of Formula 1 where Z = $-(CH_2)_{1-2}C(O)-O(CH_2)_r-$, $-(CH_2)_{1-2}C(O)-NR^3(CH_2)_r-$ and $-(CH_2)_2SO_2-NR^3(CH_2)_r-$.



Scheme V outlines the preparation of variations of Z that are not readily prepared by the strategies in Schemes III and IV. Compound **13** is available by the routes developed in Schemes I and II by replacing the primary amine NH2ZAB with O-t-butyldimethylsilyl-2-aminoethanol or its propanol homolog. Jones oxidation of **13** gives corresponding carboxylic acid which is then transformed to the acid chloride **14** by one of the methods outlined in the preceding discussion. The ester **15** is prepared by reaction of **14** with an alcohol derivative of A under conditions similar to those detailed for the preparation of ester **2** in Scheme III. The amide **16** is available by the reaction of **14** with an amine derived from A

under conditions similar to those used for the formation of amide **8** found in Scheme IV. The sulfonyl chloride **17** of Scheme V is prepared by the alcohol to halide to sulfonic acid to sulfonyl chloride route discussed for the sulfonyl analogs of Scheme IV. Reaction of **17** with an amine derivative of A under conditions used for the formation of **11** in Scheme IV gives the sulfonamide **18** of Scheme V.

<u>Scheme VI:</u> Methods to incorporate B where B = X-Y.



In Scheme VI two approaches to the incorporation of group B are outlined; in each case it is assumed that the starting structures are suitably protected to accommodate the chemistry that follows. It is also understood that both approaches may not be equivilent and, for purposes of compatibility with the chemistry that follows, one approach may have certain advantages over the other. It is further assumed that groups A and B have been selected to be derivatives of A and B that contain functionality suitable for the chemistry contemplated. Groups A and B are available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practioners skilled in the art of organic synthesis. The required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practioners skilled

in the art of organic synthesis. In the tables that follow the chemistry required to effect the coupling of A to B is outlined.

Table 1: Preparation of Amide, Ester, Urea, Sulfonamide and Sulfamide linkages between A and B.

Rxn. No.	if A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
1	$A-NHR^3$ as a substituent	ClC(O)-Y	$A-NR^3-C(O)-Y$
2	a secondary NH as part of a ring or chain	ClC(O)-Y	A-C(O)-Y
3	A-OH as a substituent	ClC(O)-Y	A-O-C(O)-Y
4	$A-NHR^3$ as a substituent	$ClC(O)-CR^3R^{3'}-Y$	$A-NR^3-C(O)-CR^3R^{3'}-Y$
5	a secondary NH as part of a ring or chain	$ClC(O)-CR^3R^{3'}-Y$	$A-C(O)-CR^3R^{3'}-Y$
6	A-OH as a substituent	$ClC(O)-CR^3R^{3'}-Y$	$A-O-C(O)-CR^3R^{3'}-Y$
7	$A-NHR^3$ as a substituent	$ClC(O)NR^3-Y$	$A-NR^3-C(O)NR^3-Y$
8	a secondary NH as part of a ring or chain	$ClC(O)NR^3-Y$	$A-C(O)NR^3-Y$
9	A-OH as a substituent	$ClC(O)NR^3-Y$	$A-O-C(O)NR^3-Y$
10	$A-NHR^3$ as a substituent	$ClSO_2-Y$	$A-NR^3-SO_2-Y$
11	a secondary NH as part of a ring or chain	$ClSO_2-Y$	$A-SO_2-Y$
12	$A-NHR^3$ as a substituent	$ClSO_2-CR^3R^{3'}-Y$	$A-NR^3-SO_2-CR^3R^{3'}-Y$

13	a secondary NH as part of a ring or chain	$ClSO_2-CR^3R^{3'}-Y$	$A-SO_2-CR^3R^{3'}-Y$
14	$A-NHR^3$ as a substituent	$ClSO_2-NR^3-Y$	$A-NR^3-SO_2-NR^3-Y$
15	a secondary NH as part of a ring or chain	$ClSO_2-NR^3-Y$	$A-SO_2-NR^3-Y$
16	A-C(O)Cl	HO-Y as a substituent	A-C(O)-O-Y
17	A-C(O)Cl	NHR^3-Y as a substituent	$A-C(O)-NR^3-Y$
18	A-C(O)Cl	a secondary NH as part of a ring or chain	A-C(O)-Y
19	$A-CR^3R^{3'}C(O)Cl$	HO-Y as a substituent	$A-CR^3R^{3'}C(O)-O-Y$
20	$A-CR^3R^{3'}C(O)Cl$	NHR^3-Y as a substituent	$A-CR^3R^{3'}C(O)-NR^3-Y$
21	$A-CR^3R^{3'}C(O)Cl$	a secondary NH as part of a ring or chain	$A-C(R^3)_2C(O)-Y$
22	$A-SO_2Cl$	NHR^3-Y as a substituent	$A-SO_2-NR^3-Y$
23	$A-SO_2Cl$	a secondary NH as part of a ring or chain	$A-SO_2-Y$
24	$A-CR^3R^{3'}SO_2Cl$	NHR^3-Y as a substituent	$A-CR^3R^{3'}SO_2-NR^3-Y$
25	$A-CR^3R^{3'}SO_2Cl$	a secondary NH as part of a ring or chain	$A-CR^3R^{3'}SO_2-Y$

The chemistry of Table 1 can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from -20°C to the reflux point of the solvent and with or without a trialkylamine base.

Table 2: Preparation of ketone linkages between A and B.

Rxn. No.	if A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
1	A-C(O)Cl	BrMg-Y	A-C(O)-Y
2	A-$CR^3R^{3'}$C(O)Cl	BrMg-Y	A-$CR^3R^{3'}{}_2$C(O)-Y
3	A-C(O)Cl	BrMg$CR^3R^{3'}$-Y	A-C(O)$CR^3R^{3'}$-Y
4	A-$CR^3R^{3'}$C(O)Cl	BrMg$CR^3R^{3'}$-Y	A-$CR^3R^{3'}$C(O)$CR^3R^{3'}$-Y

The coupling chemistry of Table 2 can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at 0°C to the reflux point of the solvent. This Grignard reagent can be reacted directly under very controlled conditions, that is low temeprature (-20°C or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide•dimethyl sulfide complex in dimethyl sulfide as a solvent or with a varient thereof. Other methods available include transforming the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 (1955) 601) or a coupling mediated by $Fe(acac)_3$ according to Fiandanese et al.(Tetrahedron Lett., (1984) 4805), or a coupling mediated by manganese (II) catalysis (Cahiez and Laboue, Tetrahedron Lett., 33(31), (1992) 4437).

Table 3: Preparation of ether and thioether linkages between A and B

Rxn. No.	if A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
1	A-OH	Br-Y	A-O-Y
2	A-$CR^3R^{3'}$-OH	Br-Y	A-$CR^3R^{3'}$O-Y
3	A-OH	Br-$CR^3R^{3'}$-Y	A-O$CR^3R^{3'}$-Y
4	A-SH	Br-Y	A-S-Y

5	A-$CR^3R^{3'}$-SH	Br-Y	A-$CR^3R^{3'}$S-Y
6	A-SH	Br-$CR^3R^{3'}$-Y	A-$SCR^3R^{3'}$-Y

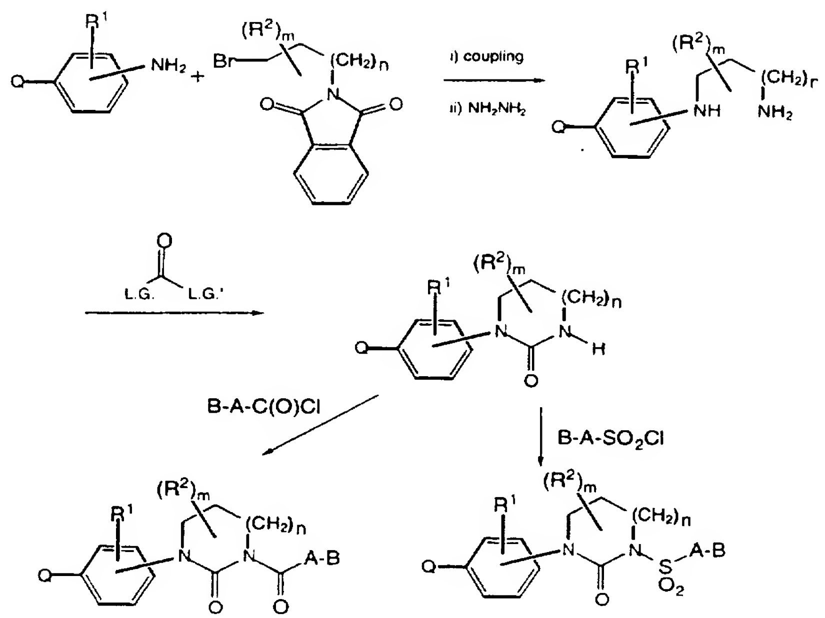
The ether and thioether linkages of Table 3 can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at temperature ranging from ambient temperature to the reflux point of the solvent used.

Table 4: Preparation of -SO- and -SO2- linkages from thioethers of Table 3.

Rxn. No.	if the starting material is:	and it is oxidized with Alumina (wet)/ Oxone (Greenhalgh, Synlett,(1992) 235) the product is:	and it is oxidized with m-chloroper-benzoic acid (Satoh et al., Chem. Lett. (1992) 381, the product is:
1	A-S-Y	A-S(O)-Y	A-SO_2-Y
2	A-$CR^3R^{3'}$S-Y	A-$CR^3R^{3'}$S(O)-Y	A-$CR^3R^{3'}SO_2$-Y
3	A-$SCR^3R^{3'}$-Y	A-S(O)$CR^3R^{3'}$-Y	A-$SO_2CR^3R^{3'}$-Y

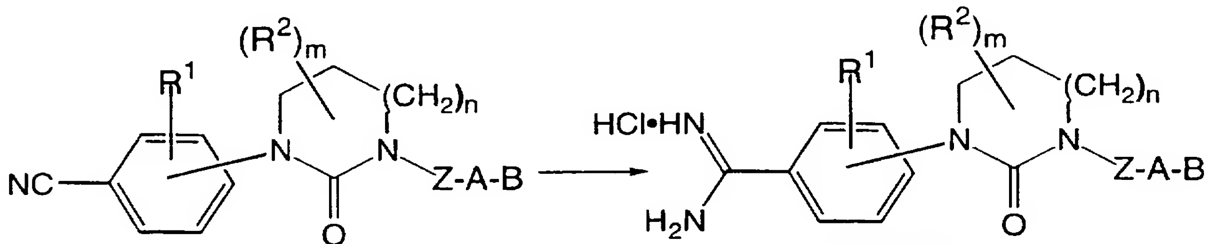
The thioethers of Table 3 serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table 4. A combination of wet alumina and oxone provides a reliable reagent for the oxidation of the thioether to the sulfoxide while m-chloroperbenzoic acid oxidation will give the sulfone.

Scheme VII: Preparation of analogs where Z = -C(O)- or $-SO_2$.



A cyclic urea precursor of Formula 1 which is suitable for the preparation of analogs where Z = -C(O)- or $-SO_2-$ can be synthesized by an adaptation of the chemistry outlined in Scheme I. The approach in Scheme VII makes use of a N-hydrazino-alkylbromide as the alkylating agent for the aniline derivative. The alkylation product is then deprotected according to a method proscribed by Greene and Wutts and cyclized by treatment of the resulting diamine with phosgene or one of its equivilents. The resulting cyclic urea can be treated with a strong base such as sodium hydride or potassium t-butoxide in an aprotic solvent like dimethyl formamide, dimethylsulfoxide or toluene. This mixture is quenched with an acid chloride or sulfonyl chloride analog of A-B at a temperature ranging from -78°C to the reflux point of the solvent.

Scheme VIII: The Pinner method to transform the cyclic urea precursor where Z = -CN to Formula 1.

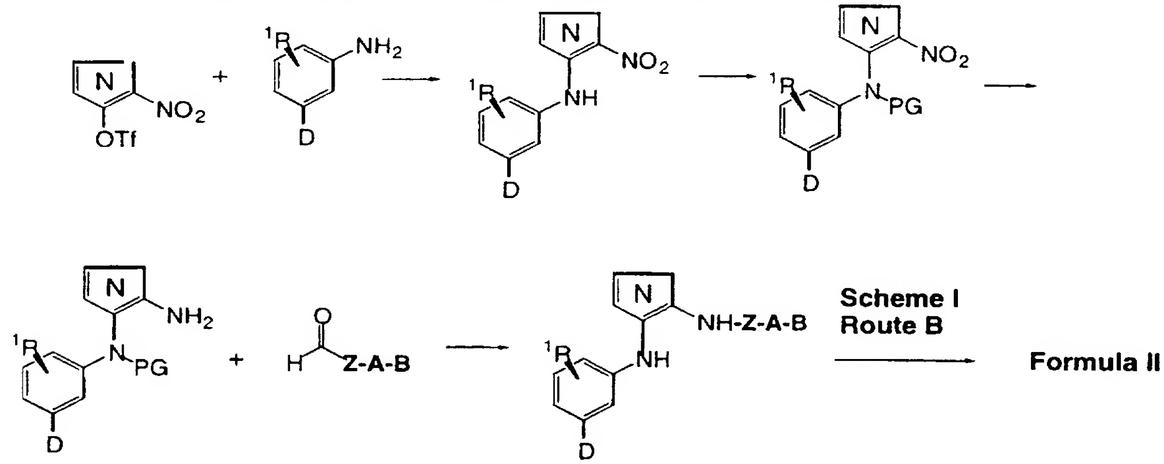


Formula 1

The final transformation of the cyclic urea precursor of Formula 1 prepared in Schemes I to VII to Formula 1 is outlined in Scheme VIII. The preferred method was first described by Pinner and Klein (*Ber.*, **10**, 1889 (1877); for a more recent review see: Decroix, *J. Chem. Res.*, 134 (1978)). By this method the nitrile is dissolved in an anhydrous alcohol or a mixture of 1 equivalent or greater of an alcohol and an anhydrous aprotic co-solvent such as a chlorohydrocarbon or an acetate ester of the selected alcohol (i.e., methyl acetate for methyl alcohol). Typically, this mixture is cooled below ambient temperature and dry hydrogen chloride gas is added slowly to the reaction mixture until the solvent is saturated. This saturated solution is sealed and stirred at ambient temperature or lower to form an imidate intermediate which is isolated and characterized. The imidate is then dissolved in a dry alcohol solvent and excess ammonia in the form of a gas, a standardized ammonia/alcohol solution, solid ammonium acetate or ammonium carbonate is added. The crude compound is conveniently purified by reverse phase HPLC or recrystallization to give the cyclic urea defined by Formula 1.

Scheme IX outlines the general route for the preparation of 5-membered aryl- or heteroaryl-fused examples of Formula II. The preparation of the biaryl amine intermediate can be accomplished by the palladium catalyzed coupling of the substituted aniline to the triflate ester according to the method of Louie et. al., (*J. Org. Chem.* **1997**, *62*, 1268-1273).

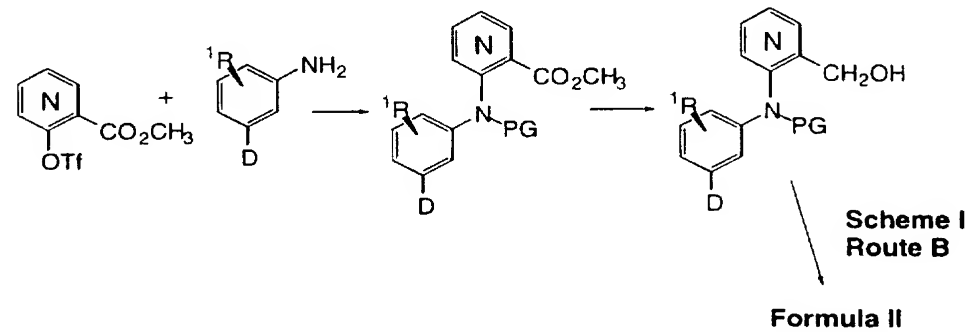
Scheme IX: Preparation of precursors to 5-membered heteroaryl-fused examples of Formula II



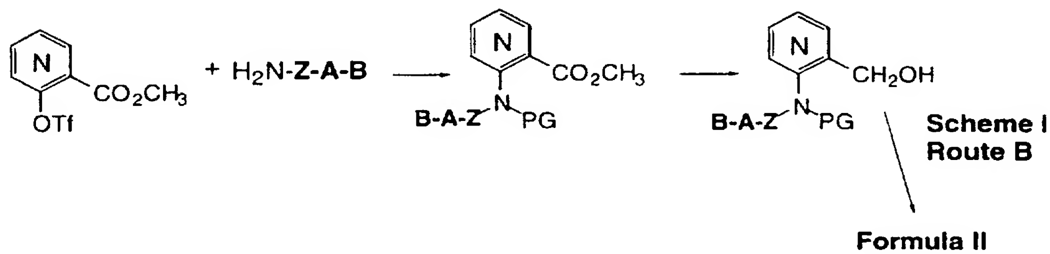
The aniline nitrogen can then be protected as a carbamate, the nitro group reduced to the amine. This amine can be coupled with a Z-A-B group in which Z incorporates a carbonyl group, such as an aldehyde, which can be used as a reactive partner in a reductive alkylation of the newly generated amine. The resulting intermediate can then be processed according to the art described for Route B of Scheme I.

Scheme X: Preparation of precursors to 6-membered aryl- or heteroaryl-fused examples of Formula II

Route A



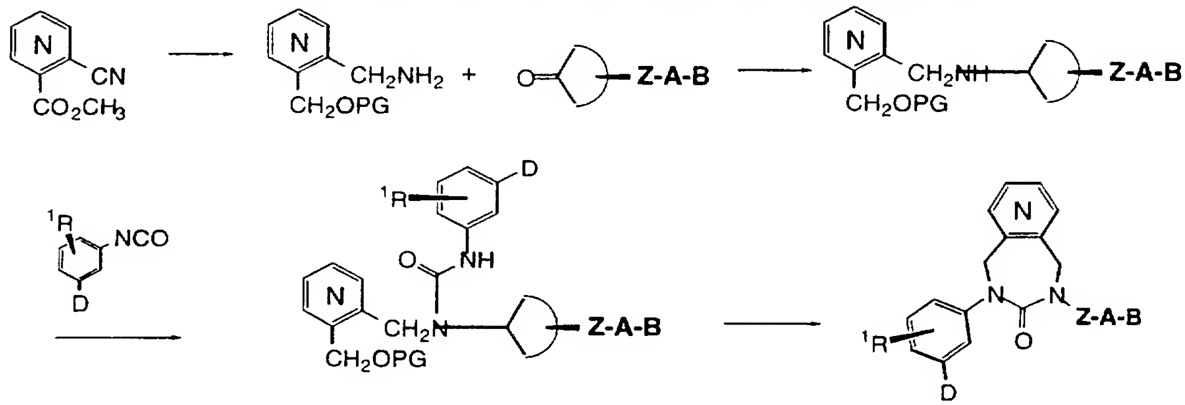
Route B



The steps which can be used for the regiocontrolled preparation of both isomers of the 6-membered aryl- or heteroaryl-fused examples of Formula II is outline in Routes A and B of Scheme X. One regioisomer is available by applying the chemistry developed by Louie et al. to the triflate of the salicylate ester in Route A. Following protection of the resulting biaryl amine, the ester can be reduced by lithium borohydride or some other compatible hydride reducing agent and then processed further as outline in Route B of Scheme I.

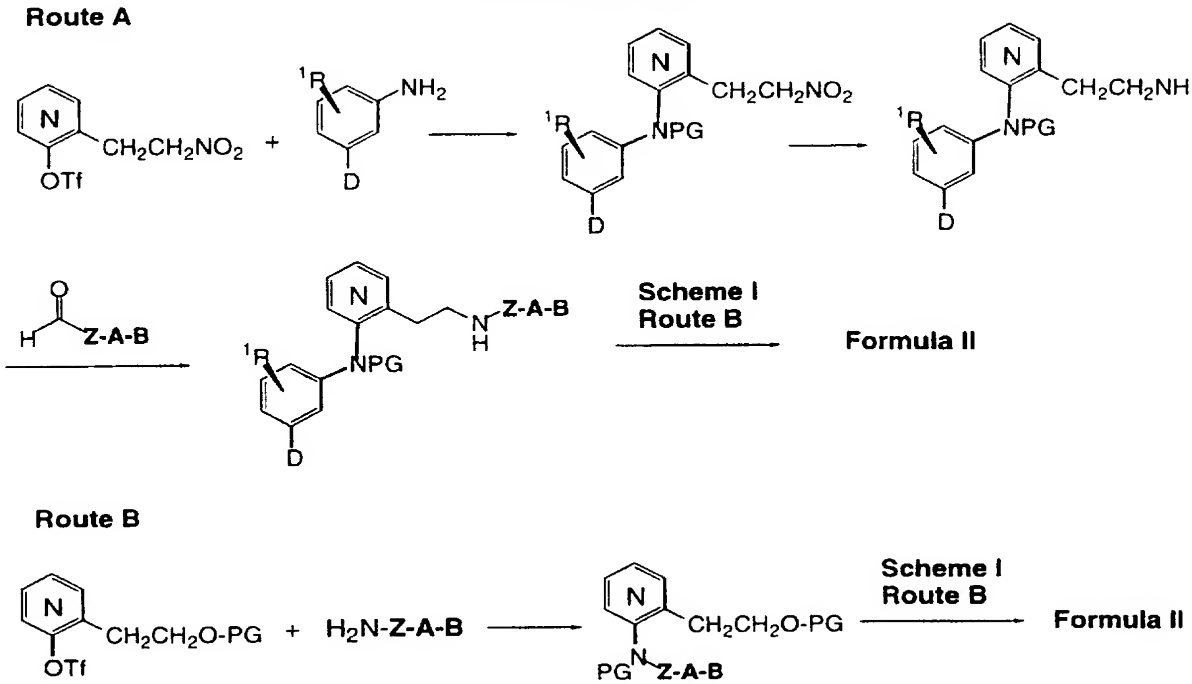
The alternative regioisomer of Formula II contemplated by this invention can be prepared according to Route B of Scheme X. To effect the palladium catalyzed coupling of the H2N-Z-A-B group with the triflate salicylate ester the conditions reported by Wolfe and Buchwald ($Pd(OAc)_2$, BiNAP, NaO-t-Bu, toluene; *J. Org. Chem.* **1997**, *62*, 1264-1267) are optimal. The amine coupling product is then suitably N-protected and the ester functionality is reduce to the benzylic alcohol. This intermediate is then treated further according to the methods outlined in Scheme I, Route B.

Scheme XI: **Preparation of precursors to 7-membered aryl- or heteroaryl-fused examples of Formula II**



Scheme XI describes the route used to prepare a precursor to one regioisomer of the 7-membered aryl- or heteroaryl-fused example of Formula II. The point of departure is usually the 2-cyano substituted aryl- or heteroaryl-ester. Lithium aluminum hydride reduction of these compounds leads to the corresponding amino alcohol which can then be selectively O-protected with a silyl protecting group, preferably the t-butyl dimethylsilyl group. This material is now ready for reductive alkylation by a Z-A-B group in which Z- contains a carbonyl compound such as an aldehyde, ketone or cyclic ketone. In our experience this transformation can best be performed using a mixture of sodium cyanoborohydride and zinc chloride in tetrahydrofuran solvent. Following reductive alkylation the resulting secondary amine is reacted with an aryl isocyanate in an inert solvent such as dimethylformamide. The isocyanate addition product can then be O-deprotected, and the benzylic alcohol be transformed to the benzylic chloride with a mixture of methanesulfonyl chloride and triethylamine in chloroform or dichloromethane. The benzylic chloride is then cyclized to the 7-membered ring precursor to Formula II with sodium hydride in dimethylformamide at 0 °C.

Scheme XII: Preparation of precursors to alternative regioisomers of 7-membered aryl- or heteroaryl-fused examples of Formula II



Routes to alternative regioisomers for 7-membered aryl- or heteroaryl-fused examples of Formula II are demonstrated in Scheme XII. In Route A, the phenethylnitro triflate can undergo a palladium catalyzed coupling with the aniline analog according to the procedure of Louie et al. The coupled product is then N-protected, usually as a carbamate or amide, then the nitro group is reduced to the amine by catalytic hydrogenation or with tin(II) chloride in aqueous or alcohol solvent. A Z-A-B group in which Z- incorporates a carbonyl functionality can then be used as a partner in a reductive alkylation with the primary amine function under the conditions described previously. This intermediate can then be submitted to the chemistry described in Scheme I, Route B to obtain a compound of Formula II. Route B describes the coupling of a protected phenethyl alcohol triflate with an amine containing Z-A-B group under the conditions recommended by Wolfe and Buchwald. This product is then N-protected as a suitable carbamate or amide and then processed by the chemistry described in Route B of Scheme I.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration fo the invention and are not intended to be limiting thereof.

Examples

The synthesis of representative compounds according to the invention is described in further detail below with reference to the following specific, but non-limiting examples.

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "d" for doublet, "dd" for doublet of doublets, "DAST" for diethylaminosulfur trifluoride, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H" for hydrogen or hydrogens, "hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "TLC" for thin layer chromatography.

EXAMPLE 1

Preparation of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea

4-(2-Hydroxyethyl)amino-1-benzylpiperidine: A mixture of 4-amino-1-benzylplperidine (1.0 g, 5.3mmol, 1.1 mL) and bromoethanol (0.662g, 5.3mmol, 0.375 mL) was stirred under a N_2 atmosphere for 18 h at ambient temperature. This material was used in directly in the next step (1.82 g). LRMS $(M+H)^+$ m/z 235.

N-(3-Cyanophenyl)-N'-(2-hydroxyethyl)-N'-(1-benzylpiperidin-4-yl)urea: To a stirred solution of 4-(2-hydroxyethyl)-amino-1-benzylpiperidine (1.82 g), and triethylamine (0.789g, 7.8mmol) in DMF (50 mL) was added 3-cyanophenylisocyanate (1.12g, 7.8 mmol). This mixture was heated at 60°C for 18 under a N_2

atmosphere. The reaction was diluted with water and extracted with ethyl acetate, dried with $MgSO_4$, filtered and concentrated to give the desired product, N-(3-cyanophenyl)-N'-(2-hydroxyethyl)-N'-(1-benzylpiperidin-4-yl)urea (2.04g, 5.3 mmol). LRMS $(M+H)^+$ m/z 379.

N-(3-Cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea: To a stirred solution of N-(3-cyanophenyl)-N'-(2-hydroxyethyl)-N'-(1-benzylpiperidin-4-yl)urea (2.04g, 5.3 mmol) in chloroform at -10°C was added a few drops of pyridine followed by thionyl chloride (0.702g, 5.9mmol). This mixture was stirred for 2 h then heated at reflux for 1h. It was concentrated in vacuo, dissolved in ethanol (50 ml) and a solution of potassium hydroxide (10 %) in ethanol (15 mL) was added and refluxed for 2h. The mixture was cooled then evaporated; it was dissoved in ethyl acetate, washed with water and brine then dried ($MgSO_4$). After removal of the solvent, the residue was purified by silica gel chromatography using ethyl acetate as the eluant. There was obtained 0.59 g of N-(3-cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea. LRMS $(M+H)^+$ m/z 361.

N-(3-Amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea: A stirred solution of N-(3-cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea (56 mg) in anhydrous methanol (10 ml) was cooled to 0°C and saturated with dry hydrogen chloride gas. This mixture was tightly stoppered and stirred at ambient temperature for 18 h. The solution was evaporated to dryness and the residual hydrogen chloride gas removed by pumping on the imidate salt for 18 h. The imidate was dissolved in anhydrous methanol (10 ml) and ammonium acetate (100 mg) was added. The mixture was stirred at ambient temperature for 24 h, then evaporated to give 55 mg of crude product. Purification of this material by reverse phase HPLC gave 26 mg of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea as the bis-trifluoroacetic acid salt; HRMS Calc. 378.229386, found 378.229774; ^1H NMR (CD_3OD) d: 2.05-2.21 (m, 4H), 3.18 (dd, 2H, J= 11 Hz, J=6.0Hz), 3.58 (dd,

4H, J=11 Hz, J= 6.0 Hz), 3.98 (t, 2H, J= 7.5 Hz), 4.02 (m,1H), 4.32 (s, 1H), 7.45 (m, 7H), 7.81 (d,1H, J= 7.5 Hz), 8.01 (s,1H).

EXAMPLE 2

Preparation of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclohexylurea

4-(3-Hydroxypropyl)amino-1-benzylpiperidine: This material was prepared in the same fashion as its lower homolog 4-(2-hydroxyethyl)amino-1-benzylpiperidine using 3-bromopropanol rather than 2-bromoethanol.

N-(3-Amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclohexyl-urea: This material was prepared from 4-(3-hydroxypropyl)-amino-1-benzylpiperidine by the same route employed in the synthesis of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea. There was obtained 26 mg of the desired product as the bis-tifluoroacetic acid salt after purification by reverse phase HPLC. LRMS $(M+2H)^{2+}$ m/z 196.7, $(M+H)^{+}$ m/z 392; ^{1}H NMR (CD_3OD): d 2.23 (m, 6H), 3.21 (bt, 2H), 3.58 (t, 2H, J= 5.12 Hz), 3.62 (m, 2H), 4.39 (m, 3H), 4.53 (t, 2H, J= 5.12Hz), 7.51 (m, 5H), 7.62-7.78 (m, 3H), 7.81 (s, 1H).

EXAMPLE 3

Preparation of N-(3-amidinophenyl)-N'-(4-amidinophenyl)cyclo-heptylurea

N-(3-cyanophenyl)-N'-(4-cyanophenyl)urea: m-Cyanoaniline (0.5 g, 3.38 mmol) and p-cyanophenylisocyanate (0.49 g, 3.38 mmol) were dissolved in dimethylformaide (8 ml) and triethylamine (1 ml). The reaction was stirred at ambient temperature under a nitrogen atmosphere for 24 h. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with water (3x), brine, dried ($MgSO_4$) and concentrated to give a amorphous solid. This was triturated to a crystalline white solid with ethyl ether. This solid was filtered and washed with ether to give

N-(3-cyanophenyl)-N'-(4-cyanophenyl)urea as a white powder (0.92 g, mp 183-5°C); LRMS $(M+H)^+$ m/z 280, $(M+NH_4)^+$ m/z 297; ^{1}H NMR (DMSO-d_6): 9.32(s, 1H), 9.21(s, 1H), 7.97(s, 1H), 7.75-7.6(m, 5H), 7.55-7.4(m, 2H).

N-(3-cyanophenyl)-N'-(4-cyanophenyl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(4-cyanophenyl)urea (0.25 g, 0.95 mmol) was dissolved in DMF (2 ml) and added to a cooled slurry of sodium hydride (0.80 g, 2.0 mmol, hexane washed to remove the mineral oil) in dimethylformamide (25 ml) under a nitrogen atmosphere. After strirring for 15 min, 1,4-dibromobutane (0.25g, 0.95 mmol) was added slowly. The reaction was stirred at 0°C for 1h and then allowed to warm to 75°C for 3 h. To the reaction additional sodium hydride was added and the reaction was heated to 75°C for an additional 6 h. The reaction was allowed to cool to ambient temperature, was poured into 1N HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried ($MgSO_4$) and concentrated to give a viscous oil. The oil was purified by flash chromatography on silica gel eluting with methylene chloride: ethyl acetate 95:5 to give N-(3-cyanophenyl)-N'-(4-cyanophenyl)cycloheptylurea as an oil (0.075 gm 0.24 mmol); LRMS $(M+H)^+$ m/z 317; ^{1}H NMR ($CDCl_3$): 7.7-7.45(m, 6H), 7.4(d, 2H), 3.82(m, 4H), 1.95(m, 4H).

N-(3-amidinophenyl)-N'-(4-amidinophenyl)cycloheptylurea: Dry hydrogen chloride gas was bubbled through an ice cooled solution of N-(3-cyanophenyl)-N'-(4-cyanophenyl)cycloheptyl-urea (0.065 g, 0.21 mmol) in anhydrous ethanol (5 ml) under a nitrogen atmosphere for 15 min. The reaction was stoppered and allowed to warm to ambient temperature and stir overnight. The reaction was concentrated in vacuo to give a white amorphous solid. This was dissolved in anhydrous ethanol (5 ml) and ammonium carbonate (0.118 g, 1.23 mmol) was added. The reaction was stirred under a nitrogen atmosphere at ambient temperature overnight. The reaction mixture was concentrated in vacuo to give a white solid. The product was purfied by HPLC on a Vydec® C-18 column eluting with solvent

mixture A (acetonitrile: water:TFA 80:20:0.3) and solvent mixture B (water: TFA 99.7:0.3) using a gradient starting with A:B at 3:97 and changing to A:B at 70:30 over 20 minutes. The major fraction was concentrated to give N-(3-amidinophenyl)-N'-(4-amidinophenyl)cycloheptylurea as a white solid (mp204-206°C); LRMS $(M+H)^+$ m/z 351, $(M+2H)^{+2}$ m/z 176.2; HRMS calc. 351.1933, found 351.1936; ^{1}H NMR (DMSO-d_6): 9.4(bs, 2H), 9.2(broad s, 2H), 9.18 (broad s, 2H), 7.95 (broad s, 2H), 7.8-7.5(m, 6H), 7.47 (d, 2H), 3.9(bd, 4H), 1.83(m, 4H).

EXAMPLE 4

Preparation of N-(3-amidinophenyl)-N'-((4-amidinophenyl)methyl)cycloheptylurea

N-(3-cyanophenyl)-N'-((4-cyanophenyl)methyl)urea: m-Cyanophenyl isocyanate (2.0 g, 13.9 mmol) and triethylamine (3.09 g, 30.5 mmol) in dimethylformamide (30 ml) was cooled to 0°C and p-cyanobenzylamine hydrogen chloride (2.3 g, 13.9 mmol) in dimethylformamide (10 ml) was added dropwise. The reaction was thawed to ambient temperature and was stirred for 18 h. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with 1N HCl and brine, then dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography on silica gel with 1:1 hexane:ethyl acetate as an eluent; there was obtained 0.54 g of pure N-(3-cyanophenyl)-N'-((4-cyanophenyl)methyl)urea; LRMS $(M+H)^+$ m/z 294.

N-(3-cyanophenyl)-N'-((4-cyanophenyl)methyl)cycloheptylurea: To a suspension of sodium hydride (0.29 g of a 60 % suspension in mineral oil, 7.28 mmol) in dimethylformamide (45 ml) at ambient temperature was added a dimethylformamide solution (5 ml) of N-(3-cyanophenyl)-N'-((4-cyanophenyl)-methyl)urea (0.67 g, 2.43 mmol). This mixture was stirred for 30 min before 1,4-dibromobutane (1.05 g, 4.85 mmol) in dimethylformamide (10 ml) was added over 20 min. The reaction was then heated at 70°C for 1 h, after which analysis by thin layer chromatography (1:2 hexane:ethyl acetate) demonstrated that

all of the starting urea had been consumed. The cooled reaction mixture was poured into ice water and extracted with ethyl acetate (3x). The extract was washed with 1N HCl and brine, then dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography on a column of silica gel with 1:1 hexane:ethyl acetate as the eluent. There was obtained 0.47 g of pure N-(3-cyanophenyl)-N'-((4-cyanophenyl)methyl)cycloheptyl-urea; LRMS: $(M+H)^+$ m/z 331.

N-(3-amidinophenyl)-N'-((4-amidinophenyl)methyl)cycloheptyl-urea: N-(3-Cyanophenyl)-N'-((4-cyanophenyl)methyl)cycloheptylurea (0.47 g, 1.42 mmol) was dissolved in a mixture of anhydrous chlorform (25 ml) and anhydrous methanol (10 ml). This solution was cooled to 0°C and slowly saturated with dry hydrogen chloride gas. The reaction vessel was securely stoppered and stored in a refrigerator for 18 h; the solvent was removed *in vacuo* and there was obtained 0.59 g of the imidate as the hydrogen chloride salt; LRMS: $(M+H)^+$ m/z 396.

The imidate prepared above (0.59 g) was stirred in anhydrous methanol (25 ml) with ammonium carbonate (0.72 g, 7.49 mmol). After 72 h the solvent was removed *in vacuo* and the residue dissolved in water. The aqueous solution was washed with ethyl ether (3x), then the water removed by lyophillization. The product was purified by HPLC on a Vydec® C-18 column eluting with solvent mixture A (water: TFA 99.5:0.5) and solvent mixture B (acetonitrile: TFA 99.5:0.5) using a gradient starting with A at 100 % and changing to B at 100 % over 50 min. The fractions containing pure N-(3-amidinophenyl)-N'-((4-amidinophenyl)methyl)cycloheptylurea were collected and lyophillized to give 0.027 g of material; HRMS $(M+H)^+$ calc. 365.208985, found 365.209496.

EXAMPLE 5

Preparation of N-(3-amidinophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptylurea

N-(3-Cyanophenyl)-N'-(1-benzylpiperidin-4-yl)urea: m-Cyanophenyl isocyanate (1.0 g, 6.94 mmol) was dissolved in dimethylformamide (15 ml) and triethylamine (2 ml) under a nitrogen atmosphere, then 4-amino-1-benzyl-piperidine (1.32 g, 6.94 mmol) was added slowly. The reaction was stirred at ambient temperature for 1 h and then at 70°C for 2h. The reaction was allowed to cool to ambient temperature and partioned between water and ethyl acetate. The organic layer was washed with water (2x) and brine then dried ($MgSO_4$) and concentrated to give a white amorphous solid. The solid was triturated with ethyl ether to give a white powder. The solids was filtered, washed with ethyl ether and dried to give N-(3-cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cyclopentylurea as a white powder, (1.7 g, 74%, mp 165-6°C); LRMS $(M+H)^+$ m/z 335; ^1H NMR ($CDCl_3$): 7.62(s, 1H), 7.57(d, 1H), 7.15-7.2(M, 7H), 7.15(s, 1H), 5.05(d, 1H), 3.65(m, 1H), 3.5(s, 2H), 2.85(m,2H), 2.1(m,2H), 1.95(m, 2H), 1.45(m,2H).

N-(3-Cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(1-benzylpiperidin-4-yl)urea (0.5 g, 1.49 mmol) was dissolved in DMF (25 ml) and 1,4 dibromobutane (0.33 g, 1.49 mmol) was added under a nitrogen atmosphere. The reaction was heated to 70°C and sodium hydride (0.131 gm 3.3 mmol) was added portionwise over 20 minutes. The reaction was heated for 4 h then allowed to cool to ambient temperature. When cool, it was poured into water and extracted with ethyl acetate. The organic layer was washed water (2x) and brine, then dried ($MgSO_4$) and concentrated to give a viscous oil. The crude oil was purified by flash chromatography on silica gel eluting with methylene chloride: ethyl acetate 40:60 to give N-(3-cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea as an oil (0.37 g, 64%); LRMS $(M+H)^+$ m/z 389.4; ^1H NMR ($CDCl_3$): 7.4-7.25(m, 9H), 3.9(m, 1H), 3.57(m,

2H), 3.42(s, 2H), 3.25(m, 2H), 2.87(m, 2H), 2.03(m, 2H), 1.8-1.5(m, 8H).

N-(3-Cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea (0.1 g 0.26 mmol) was dissolved in ethanol (10 ml) and cyclohexene (2 ml). Palladium hydroxide catalyst (0.05 g) was added and the reaction was heated at reflux under a nitrogen atmosphere. After 30 min the reaction was allowed to cool to ambient temperature, filtered and concentrated to give a viscous oil. The crude product was purified by flash chromatography on silica gel by eluting with methylene chloride:methanol 85:15 with 3 % triethylamine. The product, N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea, was concentrated to give an oil which crystallized from ethyl ether (0.05 g, 48%, mp 157-8°C); LRMS $(M+H)^+$ m/z 299; ^1H NMR ($CDCl_3$): 7.5-7.3(m, 4H), 4.05(m, 1H), 3.60(m, 2H), 3.32(m, 2H), 3.17(m, 2H), 2.72(m, 2H), 2.0-1.6(m, 8H).

N-(3-Cyanophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea (0.05 g, 0.126 mmol) was dissolved in pyridine (2 ml) and 3,5-dimethylpyrazole-1-carboxamidine (0.037 g, 0.188 mmol) was added under a nitrogen atmosphere. The reaction was heated to 110°C for 6 h, then was allowed to cool and was concentrated to give a viscous amber oil. The product was purfied by HPLC on a Vydec® C-18 column eluting with solvent mixture A (acetonitrile: water:TFA 80:20:0.3) and solvent mixture B (water: TFA 99.7:0.3) using a gradient starting with A:B at 3:97 and changing to A:B at 70:30 over 15 min. The product eluted at 13.8 minutes was concentrated to give N-(3-cyanophenyl)-N'-(1-amidinopiperidin-4-yl)cyclo-heptylurea as an amorphous solid (0.036 g); LRMS $(M+H)^+$ m/z 341.

N-(3-Amidinophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptyl-urea: Dry hydrogen chloride gas was bubbled through an ice cooled solution of N-(3-cyanophenyl)-N'-(1-amidinopiperidin-4-yl)cyclo-heptylurea (0.03 g, 0.075 mmol) in anhydrous ethanol

(5 ml) for 15 min. The reaction was stoppered, allowed to warm to ambient temperature and stirred for 24 h. The reaction was concentrated to give a viscous residue which was dissolved in anhydrous ethanol and ammonium carbonate (0.06 g, 0.63 mmol) was added. The reaction was stirred over night at ambient temperature and then concentrated *in vacuo*. The crude product appeared to be about 1:2 ratio of the desired product to starting material. Pure N-(3-amidinophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptylurea was isolated by HPLC on a Vydec® C-18 column eluting with solvent mixture A (acetonitrile: water:TFA 80:20:0.3) and solvent mixture B (water: TFA 99.7:0.3) using a gradient starting with A:B at 3:97 and changing to A:B at 70:30 over 20 min, to give two major fractions: N-(3-amidinophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptylurea, the desired product eluted at 13.3 minutes, (8.2 mg); LRMS $(M+2H)^{+2}$ m/z 179.8; HRMS calc. 358.2355, found 358.2349; ^{1}H NMR (DMSO-d_6): 9.25(s, 2H), 9.0(s, 2H), 7.55-7.4(m, 4H), 7.32(s, 4H), 3.95(m, 3H), 3.65(m, 2H), 3.25(m, 2H), 3.07(m, 2H), 1.8-1.6(m, 8H).

The second fraction, eluting at 18.1 min., was the starting material N-(3-cyanophenyl)-N'-(1-amidinopiperidin-4-yl)cycloheptylurea (16.6 mg); LRMS $(M+H)^+$ m/z 341.1; HRMS calc. 341.20898, found 3341.2077; ^{1}H NMR (DMSO-d_6): 7.6(s, 1H), 7.5-7.4(m, 3H), 7.3(s, 4H), 4.0-3.9(m, 3H), 3.6(m, 2H), 3.25(m, 2H), 3.05(m, 2H), 1.8-1.55(m, 8H).

EXAMPLE 6

Preparation of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea

N-(3-Amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea: Dry hydrogen chloride gas was bubbled through an ice cooled solution of N-(3-cyanophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea (0.03 g, 0.077 mmol) in anhydrous ethanol (10 ml) under a nitrogen atmosphere for 15 min. The reaction was stoppered, allowed to warm to ambient temperature and stirred for 24 h. The reaction was concentrated to a solid

and dissolved in anhydrous ethanol (5 ml) and ammonium carbonate (0.023 g, 0.23 mmol) was added. The reaction mixture was stirred at ambient temperature overnight then was concentrated *in vacuo*. N-(3-Amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea was purified by HPLC on a Vydec® C-18 column eluting with solvent mixture A (acetonitrile: water:TFA 80:20:0.3) and solvent mixture B (water: TFA 99.7:0.3) using a gradient starting with A:B at 3:97 and changing to A:B at 70:30 over 15 min. The major fraction eluting at 15 minutes was concentrated to give N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea as an amorphous solid; LRMS $(M+H)^+$ m/z 406, $(M+2H)^{+2}$ m/z 203.8; ^1H NMR (DMSO-d_6): 9.52(broad s, 1H), 9.27(s, 2H), 9.02(s, 2H), 7.5(m, 9H), 4.3(m,m, 2H), 3.95(m, 1H), 3.67(m, 2H), 3.42(m, 2H), 3.2(m,2H), 3.1(m, 2H), 2.05-1.6(m, 8H).

EXAMPLE 7

Preparation of N-(3-amidinophenyl)-N'-(1-(α-phenethyl)piperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-(a-phenethyl)piperidin-4-yl)cycloheptylurea: N-(3-amidinophenyl)-N'-(1-(a-phenethyl)piperidin-4-yl)cycloheptylurea was prepared by a method analogous to the preparation of N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea starting with 4-amino-1-(a-phenethyl)piperidine rather than 4-amino-1-benzylpiperidine; HRMS: calc 420.276336, found 420.276129; ^1H NMR (CD_3OD) d: 1.78 (d, 3H, J= 6.95 Hz), 1.79 (m, 4H), 2.05 (m, 4H), 2.89 (m,3H), 3.38 (m, 2H), 3.76 (m,2H), 3.82 (broad d,2H), 3.92 (m,1H)4.42 (q, 1H, J= 6.95 Hz), 7.42 (broad s,5H), 7.52 (broad s, 3H), 7.60 (s, 1H).

EXAMPLE 8

Preparation of N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea

N-(3-Cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)piperidin-4-yl)urea: A mixture of 4-amino-N-(*t*-butoxycarbonyl)piperidine (0.133

mol, 30.5 g, prepared by the method of Mach, R.H. et al., J. Med. Chem. (1993) 36(23), 3707-20) and triethylamine (1.5 equivilents, 0.2 mol, 20.2 g, 27.8 ml) in dimethylformamide (230 ml) was cooled to 0°C and m-cyanophenylisocyanate (1.1 equivilents, 0.146 mmol, 21.1 g) in dimethylformamide (70 ml) was added dropwise. The reaction was stirred at ambient temperature for 18 h. It was poured into water and extracted with ethyl acetate (3x). The ethyl acetate extracts were washed with 1N HCl and brine, then dried (Na_2SO_4) and evaporated to give 43.56 g of crude material. Pure N-(3-cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)piperidin-4-yl)urea was isolated by flash chromatography on silica gel (1.2 kg) eluted with 2:1 hexane:ethyl acetate (6 L) then 1:1 heaxane ethyl acetate collected in 800 ml fractions. Fractions 9 thru 14 contained pure product, yield 21.69 g.

N-(3-Cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)piperidin-4-yl)cycloheptylurea: A mixture of sodium hydride (2.44 g of a 60 % suspension in mineral oil, 60.9 mmol) and dimethylformamide (350 ml) was stirred at ambient temperature for 5 min, then N-(3-cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)-piperidin-4-yl)urea (7.0 g, 20.3 mmol) in dimethylformamide (30 ml) was added dropwise. This mixture was stirred at ambient temperature for 30 min after which gas evolution ceased. 1,4-Dibromobutane (8.79 g, 40.6 mmol) in dimethylformamide (20 ml) was added slowly over 25 min. Following the addition of the alkylating agent the reaction mixture was heated at 70°-80°C for 3 h then was stirred at ambient temperature for 18 h. The reaction mixture was poured into water (1 L) and extracted with ethyl acetate (4 x 250 ml). The ethyl acetate extracts were washed with brine (6x), dried (Na_2SO_4) and evaporated to give 10.58 g of crude product. Pure N-(3-cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)-piperidin-4-yl)cycloheptylurea was isolated by medium pressure chromatography on a silica gel column (600 g) by eluting with 2:1 hexane:ethyl acetate to give 3.20 g of pure product.

N-(3-Cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)piperidin-4-yl)cycloheptylurea (3.2 g, 7.76 mmol) was stirred in dichloromethane (40 ml) and trifluoroacetic acid (40 ml) at ambient temperature for 1.5 h. The reaction mixture was evaporated and the residue taken up in water. The aqueous suspension was made basic (pH 11) by the dropwise addition of aqueous sodium hydroxide solution (50 %). The basic aqueous suspension was extracted with ethyl acetate (2x); the ethyl acetate extracts were washed with brine, dried (Na_2SO_4), and evaporated to give N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea (2.17 g, 7.28 mmol, 94 %). This sample was in all respects identical to the sample of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea prepared in Example 5.

N-(3-Cyanophenyl)-N'-(1-((phenyl)methane)sulfonyl)piperidin-4-yl)cycloheptylurea: N-(3-Cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea (2.07 g, 6.95 mmol) in tetrahydrofuran (100 ml) with triethylamine (7.64 mmol, 0.77 g, 1.1 ml) was cooled to 0°C and a-toluenesulfonyl chloride (1.46 g, 7.64 mmol) in tetrahydrofuran (60 ml) was added dropwise. The reaction was allowed to cool to ambient temperature and was stirred for 18 h. The solvent was removed in vacuo and the residue patitioned between water and 5:1 ethyl acetate:acetone. The organic layer was washed with 1<u>N</u> HCl and 1<u>N</u> NaOH, then brine. It was dried (Na_2SO_4) and evaporated to give 2.63 g of crude product. Purification by medium pressure liquid chromatography on a silica gel column (350 g) gave N-(3-cyanophenyl)-N'-(1-((phenyl)methane)- sulfonyl)piperidin-4-yl)cycloheptylurea (1.81 g, 4.0 mmol, 58%, mp 203-204°C); HRMS $(M+H)^+$ calc. 453.196038, found 453.198085.

N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea: A solution of N-(3-cyanophenyl)-N'-(1-((phenyl)methane)-sulfonyl)piperidin-4-yl)cycloheptylurea (1.15 g, 2.54 mmol) in anhydrous methyl acetate (300ml) was cooled to 0°C and anhydrous methanol (0.81 g, 25.4 mmol, 1.02 ml) was added. The cooled solution was

saturated with dry hydrogen chloride gas then was stoppered tightly and was left to stir at ambient temperature for 18 h. Analytical thin layer chromatography (5 % methanol in chloroform) showed complete consumption of the starting nitrile. The methyl acetate solution was diluted with ethyl ether (1.7 L) then left to form crystals in the refrigerator over 18 h. After this time, precipitation of the imidate was complete and the intermediate product was isolated as the hydrogen chloride salt by filtration. The solid imidate was pumped on for several hours to remove any residual HCl and protect the product from moisture. This procedure gave 1.27 g of imidate hydrochloride (2.43 mmol, 96 %, mp 131-134°C).

The imidate prepared above (1.27 g, 2.43 mmol) was dissolved in dry methanol (50 ml) and 2N ammonia in methanol solution (24.3 mmol, 12.15 ml) was added. This reaction was stoppered and stirred at ambient temperature for 24 h. After this time, the solvent was removed in vacuo and the 1.27 g of crude product was isolated. The major contaminant (aproximately 50 %) was the corresponding amide. This mixture was separated by HPLC on a Vydec® C-18 column eluting with solvent mixture A (water: TFA 99.5:0.5) and solvent mixture B (acetonitrile: TFA 99.5:0.5) using a gradient starting with A at 100 % and changing to B at 100 % over 50 min. The desired product, N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea, was eluted at 30 min; after collection of the fractions and lyophylization, 0.30 g of pure product was obtained as the trifluoroacetic acid salt (0.5 mmol, 20 %, mp 208-209°C); HRMS $(M+H)^+$ calc. 470.222587, found 470.219813.

The following Example 9 to 12 were prepared by essentially the same preparative methods as described above for Example 8; the only changes involved the sulfonylation or acylation of the common intermediate N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea. In each case, however, the same procedure using the appropriate sulfonylating or acylating agent in tetrahydrofuran with triethylamine was used.

EXAMPLE 9

Preparation of N-(3-amidinophenyl)-N'-(1-benzoylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-benzoylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by acylation of N-(3-cyanophenyl)-N'-(piperidin-4-In this case the title compound was prepared by acylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with benzoyl chloride folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 421.223966, found 421.222804.

EXAMPLE 10

Preparation of N-(3-amidinophenyl)-N'-(1-((phenyl)methane)carbonylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-((phenyl)methane)carbonylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by acylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with phenylacetyl chloride folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 434.255601, found 434.255065.

EXAMPLE 11

Preparation of N-(3-amidinophenyl)-N'-(1-(phenyl)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-(phenyl)sulfonylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by acylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with benzoyl chloride folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 456.206937, found 456.204189.

EXAMPLE 12

Preparation of N-(3-amidinophenyl)-N'-(1-(4-acetamidophenyl)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-(4-acetamidophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by sulfonylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with (4-acetamidophenyl)-sulfonyl chloride folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 513.228401, found 513.226577.

EXAMPLE 13

Preparation of N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-cyanophenyl)-N'-(1-(2-nitrophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea (1.5 g, 5.03 mmol) in tetrahydrofuran (30 ml) and triethylamine (1.02 g, 10.06 mmol) was cooled to 0°C.

A solution of (2-nitrophenyl)sulfonyl chloride (1.3 g, 5.86 mmol) in tetrahydrofuran (5 ml) was added dropwise and the reaction was stirred at ambient temperature for 18 h.The solvent was removed in vacuo and the residue dissolved in ehtylacetate. The ethyl acetate solution was washed with 1N HCl and brine, then dried (Na_2SO_4) and evaporated. Pure N-(3-cyanophenyl)-N'-(1-(2-nitrophenyl)sulfonylpiperidin-4-yl)cycloheptylurea was isolated by flash chromatography on silica gel by first eluting with 2:1 hexane ehtyl acetate, then 1:1 hexane ethyl acetate. There was obtained 0.71 g of the title compound; LRMS $(M+H)^+$ m/z 484.

N-(3-cyanophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: N-(3-cyanophenyl)-N'-(1-(2-nitrophenyl)sulfonylpiperidin-4-yl)cycloheptylurea (0.71 g, 1.47 mmol) in ethanol (90 ml) and water (10 ml) was stirred with zinc dust (3.2 g, 48.6 mmol) and calcium chloride (0.11 g, 0.95 mmol). This mixture was heated at reflux for

3 h then filtered hot through a Celite® pad and evaporated; 0.59 g of N-(3-cyanophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea was obtained; LRMS $(M+H)^+$ m/z 454.

N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: N-(3-cyanophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea (0.20 g, 0.44 mmol) in anhydrous chloroform (25 ml) and anhydrous methanol (10 ml) was cooled to 0°C and saturated with dry hydrogen chloride gas. The reaction vessel was securely stoppered and was stirred at ambient temperature for 18 h. The intermediate imidate was obtained as the hydrogen chloride salt (0.23 g) by removal of the solvent and residual hydrogen chloride in vacuo; LRMS $(M+H)^+$ m/z 486.

The imidate prepared above (0.23 g) and a 2N solution of ammonia in methanol (1.5 ml) were stirred in a tightly stopper flask at ambient temperature for 18 h. A mixture of the desired amidine and the corresponding amide were obtained anfter removal of the solvent. This mixture was separated by HPLC on a Vydec® C-18 column eluting with solvent mixture A (water: TFA 99.5:0.5) and solvent mixture B (acetonitrile: TFA 99.5:0.5) using a gradient starting with A at 100 % and changing to B at 100 % over 50 min. There was obtained 38 mg of the desired product N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonyl-piperidin-4-yl)cycloheptylurea; HRMS $(M+H)^+$ calc. 471.217836, found 471.218097.

The corresponding amide side product N-(3-amidophenyl)-N'-(1-(2-aminophenyl)sulfonyl-piperidin-4-yl)cycloheptylurea was also isolated (46 mg); HRMS $(M+H)^+$ calc. 472.201852, found 472.202530.

The following Example 14 to 16 were prepared by essentially the same preparative methods as described above for Example 13; the only changes involved the sulfonylation of the common intermediate N-(3-cyanophenyl)-N'-(piperidin-4-

yl)cycloheptylurea. In each case, however, the same procedure using the appropriate sulfonylating agent in tetrahydrofuran with triethylamine was used.

EXAMPLE 14

Preparation of N-(3-amidinophenyl)-N'-(1-(3-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-(3-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by sulfonylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with 3-nitrophenylsulfonyl chloride. This product was reduced by a mixture of zinc dust and calcium chloride in aqueous ethanol followed by amidine formation as described above to give the title compound; HRMS $(M+H)^+$ calc. 471.217836, found 471.219532.

EXAMPLE 15

Preparation of N-(3-amidinophenyl)-N'-(1-(4-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-(4-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by sulfonylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with 4-nitrophenylsulfonyl chloride. This product was reduced by a mixture of zinc dust and calcium chloride in aqueous ethanol followed by amidine formation as described above to give the title compound; HRMS $(M+H)^+$ calc. 471.217836, found 471.217059.

EXAMPLE 16

Preparation of N-(3-amidinophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea

N-(3-amidinophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea: In this case the title compound was prepared by sulfonylation of N-(3-cyanophenyl)-

N'-(piperidin-4-yl)cycloheptylurea with ((2-nitrophenyl)methane)sulfonyl chloride. This product was reduced by a mixture of zinc dust and calcium chloride in aqueous ethanol followed by amidine formation as described above to give the title compound; HRMS $(M+H)^+$ calc. 485.233486, found 485.235037.

EXAMPLE 17

Preparation of N-(3-amidinophenyl)-N'-(1-((2-acetamido-phenyl)methane)sulfonylpiperidin-4-yl)cycloheptylurea

N-(3-cyanophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl-piperidin-4-yl)cycloheptylurea: This material was prepared by sulfonylation of N-(3-cyanophenyl)-N'-(piperidin-4-yl)cycloheptylurea with ((2-nitrophenyl)methane)sulfonyl chloride in tetrahydrofuran and triethyl amine, as described for EXAMPLE 16. Reduction of the nitro group using zinc dust and calcium chloride in aqueous ethanol gave N-(3-cyanophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl-piperidin-4-yl)cycloheptylurea;
LRMS $(M+H)^+$ m/z 468.

N-(3-cyanophenyl)-N'-(1-((2-acetamidophenyl)methane)sulfonyl-piperidin-4-yl)cycloheptylurea: N-(3-cyanophenyl)-N'-(1-((2-aminophenyl)methane)sulfonylpiperidin-4-yl)cycloheptylurea (0.296 g, 0.63 mmol) in chloroform (30 ml) and triethylamine (0.13 g, 1.27 mmol) was cooled to 0°C and acetyl chloride (0.06 g, 0.76 mmol) was added. The reaction was allowed to warm to ambient temperature and was stirred for 6 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate and washed with 1N HCl and brine, then dried (Na_2SO_4) and evaporated. Purification by silica gel flash chromatography with 5% methanol in chloroform gave 194 mg of N-(3-cyanophenyl)-N'-(1-((2-acetamidophenyl)methane)sulfonyl-piperidin-4-yl)cycloheptylurea; LRMS $(M+H)^+$ m/z 510.

N-(3-amidinophenyl)-N'-(1-((2-acetamidophenyl)methane)-sulfonylpiperidin-4-yl)cycloheptylurea: N-(3-cyanophenyl)-N'-

(1-((2-acetamidophenyl)methane)sulfonyl-piperidin-4-yl)cycloheptylurea (0.194 g, 0.38 mmol) in anhydrous methyl acetate (25 ml) and anhydrous methanol (10 ml) was cooled to 0°C and saturated with dry hydrogen chloride gas. The reaction vessel was securely stoppered and was stirred at ambient temperature for 18 h. The intermediate imidate was obtained as the hydrogen chloride salt (0.174 g) by removal of the solvent and residual hydrogen chloride in vacuo; LRMS $(M+H)^+$ m/z 542.

The imidate prepared above (0.174 g) and a solution of ammonium acetate (0.15 g) in methanol (10 ml) were stirred at ambient temperature for 18 h. A mixture of the desired amidine and the corresponding amide were obtained after removal of the solvent. This mixture was separated by HPLC on a Vydec® C-18 column eluting with solvent mixture A (water: TFA 99.5:0.5) and solvent mixture B (acetonitrile: TFA 99.5:0.5) using a gradient starting with A at 100 % and changing to B at 100 % over 50 min. There was obtained 9.6 mg of the desired product N-(3-amidinophenyl)-N'-(1-((2-acetamidophenyl)methane)-sulfonylpiperidin-4-yl)cyclo-heptylurea; HRMS $(M+H)^+$ calc. 527.244051, found 527.246420.

The corresponding amide side product N-(3-amidophenyl)-N'-(1-((2-acetamidophenyl)methane)-sulfonylpiperidin-4-yl)cycloheptylurea was also isolated (8.5 mg); HRMS $(M+H)^+$ calc. 528.228066, found 528.236184.

EXAMPLE 18

Preparation of 1-(1-benzoylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone

1-(1-*t*-butoxycarbonylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone: A mixture of N-(3-cyanophenyl)-N'-(1-(*t*-butoxycarbonyl)-piperidin-4-yl)urea (0.50 g, 1.45 mmol) and sodium hydride (0.20 g of a 60 % suspension in mineral oil, 8.3 mmol) in dimethylformamide was stirred at ambient temperature for 30 min. then *cis*-1,4-dichloro-2-butene (0.18

g, 1.44 mmol) was added. This mixture was heated at 70°C for 4 h, after which an addition 0.2 g of 60 % sodium hydride and 0.04 g of *cis*-1,4-dichloro-2-butene was added. The mixture was heated at 70°C for an addition 2 h during which the remaining starting material was consumed. The reaction was diluted with brine (50 ml) and extracted with ethyl acetate (3x). The ethyl acetate extracts were washed with brine, then dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel, eluting with 2:1 hexane:ethyl acetate to give 0.20 g of 1-(1-*t*-butoxycarbonylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone; LRMS $(M+H)^+$ m/z 397.

1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone: 1-(1-*t*-Butoxycarbonylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone (1.32 g, 3.3 mmol) was stirred in 1:1 dichloromethane: trifluoroacetic acid (30 ml) for 4 h. This solvent was removed *in vacuo*, and 1.35 g of 1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone was obtained as the trifluoroacetic acid salt LRMS $(M+H)^+$ m/z 297.

1-(1-benzoylpiperidin-4-yl)-3-(3-cyanophenyl)-5-ethenyl-2-imidazolidinone: The free base of 1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone (1.99 g, 6.72 mmol) in tetrahydrofuran (50 ml) and triethylamine (1.36 g, 13,44 mmol) was cooled to 0°C and benzoyl chloride in tetrahydrofuran (10 ml) was added. After 4 h the reaction was complete; the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with 1<u>N</u> HCl and brine, then dried (Na_2SO_4) and evaporated. The desired product was isolated by flash chromatography using silica get and 2:1 ethyl acetate as eluent. There was obtained 0.63 g of pure 1-(1-benzoylpiperidin-4-yl)-3-(3-cyanophenyl)-5-ethenyl-2-imidazolidinone; LRMS $(M+H)^+$ m/z 401.

1-(1-benzoylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone: 1-(1-Benzoylpiperidin-4-yl)-3-(3-cyanophenyl)-5-ethenyl-2-imidazolidinone (0.30 g, 0.75 mmol) in anhydrous 4:1 chloroform:methanol (25 ml) was cooled to 0°C and saturated with dry hydrogen chloride gas. The reaction vessel was stoppered securely then left to stand at 10°C for 72 h. The solvent was removed *in vacuo* to give 0.33 g of the imidate as the hydrogen chloride salt (0.75 mmol); LRMS $(M+H)^+$ m/z 433.

The imidate prepared above (0.33 g, 0.75 mmol) was dissolved in anhydrous methanol (10 ml) and ammonium carbonate (0.36 g, 3.76 mmol) was added. This mixture was stirred at ambient temperature for 18 h, then the solvent was removed *in vacuo*. The residue was dissolved in water (10 ml) and washed with diethyl ether (3x). The aqueous layer was lyophillized and the crude product was purified by HPLC on a Vydec® C-18 column eluting with solvent mixture A (water: TFA 99.5:0.5) and solvent mixture B (acetonitrile: TFA 99.5:0.5) using a gradient starting with A at 100 % and changing to B at 100 % over 50 min. The fractions containing pure 1-(1-benzoylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone were collected and lyophillized to give 0.090 g of material; HRMS $(M+H)^+$ calc. 418.224300, found 418.223792.

The following Example 19 and 20 were prepared by essentailly the same preparative methods as described above for Example 18; the only changes involved the sulfonylation of the common intermediate 1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone. In each case, however, the same procedure using the appropriate acylating or sulfonylating agent in tetrahydrofuran with triethylamine was used.

EXAMPLE 19

Preparation of 1-(1-((phenyl)methane)sulfonyl)piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone

In this case the title compound was prepared by sulfonylation of 1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone with α-toluene sulfonyl chloride in tetrahydrofuran with triethylamine folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 468.206937, found 468.204978.

EXAMPLE 20

Preparation of 1-(1-phenylsulfonylpiperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone

In this case the title compound was prepared by sulfonylation of 1-(piperidin-4-yl)-3-(3-amidinophenyl)-5-ethenyl-2-imidazolidinone with phenylsulfonyl chloride in tetrahydrofuran with triethylamine folowed by amidine formation as described above; HRMS $(M+H)^+$ calc. 454.191287, found 454.191418.

EXAMPLE 21

Preparation of 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one

N-[methyl(2-((t-butyldimethylsilyloxy)methyl)phenyl)]-N-[(N-carbo-t-butoxy)piperidin-4-yl]amine: A solution of methyl-2-cyanobenzoate (10 g, 62.11 mmol) in ethyl ether (300 mL) was added dropwise to a slurry of lithium aluminum hydride in ethyl ether (200 mL). After the addition was complete, more ether was added (200 mL) and the mixture heated at reflux for 2h. The cooled reaction mixture was quenched by careful addition of succesive amounts of water (7.1 mL), 1<u>N</u> sodium hydroxide solution (7.1 mL) and water (21.3 mL). The reaction was filtered and evaporated to give 6.96 g (50.8 mmol) of 2-(aminomethyl)benzyl alcohol. This material was carried on without further purification.

The material from above was dissolved in tetrahydrofuran (140 mL) and cooled to 0^{o}C. To this mixture was added imidazole (1.3 equivilents, 4.5 g, 66.04 mmol) and t-butyldimethylsilyl chloride (1.05 equivilents, 8.04 g, 53.34 mmol). The reaction mixture was stirred at ambient temperature for 18 h then was diluted with water (500 mL) and extracted with ethyl ether (3 x 150 mL). The ether extract was dried ($MgSO_4$) and evaporated to give 10.78 g (41 mmol) of the t-butyldimethyl-silyl ether of 2-(aminomethyl)benzyl alcohol.

To a mixture of the t-butyldimethylsilyl ether prepared above (7.77 g, 29.5 mmol) and N-(carbo-t-butoxy)piperidin-4-one (5.88 g, 29.5 mmol) in methanol at 0^{o}C was added zinc chloride (4.02 g, 29.5 mmol) followed by sodium cyanoborohydride (2.04 g, 32.45 mmol). The reaction was thawed to ambient temperature and stirred for 18 h. After this time, the reaction was judged to be complete by TLC (20% methanol in chloroform); the solvent was removed by distillation *in vaccuo* and the residue partitioned between ethyl acetate and 1<u>N</u> hydrochloric acid solution. The ethyl acetate layer was washed with brine and dried ($MgSO_4$) then evaporated to give 11.66 g (26.87 mmol) of N-[methyl(2-((t-butyldimethylsilyloxy)methyl)phenyl)]-N-[(N'-carbo-t-butoxy)piperidin-4-yl]amine.

N-[methyl(2-(chloromethyl)phenyl)]-N-[(N'-carbo-t-butoxy)piperidin-4-yl]-(3-cyano)benzamide: A mixture of 11.66 g (26.87 mmol) of N-[methyl(2-((t-butyldimethylsilyloxy)-methyl)phenyl)]-N-[(N-carbo-t-butoxy)piperidin-4-yl]amine and 3-cyanophenyl isocyanate (3.87 g, 26.87 mmol) in dimethyl-formamide (100 mL) was stirred at ambient temperature for 24 h. The reaction was judged to be complete by TLC (5% methanol in chloroform) and diluted with brine (500 mL). The suspension was extracted with ethyl acetate (150 mL) and the ethyl acetate extracts were washed with brine (5 x 100 mL) then dried ($MgSO_4$) and evaporated to give 14.54 g of crude material. This material was purified further by elution from

a 400 gram column of silica gel with a mixture of ethyl acetate and hexane; the material isolated from the eluent was 11.66 g (20.17 mmol) of the pure isocyanate addition product.

A tetrahydrofuran solution (200 mL) of the purified isocyanate addition product (11.5 g, 20 mmol) was treated with solid tetra-n-butylammonium fluoride (5.75 g, 22 mmol). The reaction was complete in 30 min (TLC, 1:1 hexane:ethyl acetate) whereupon the solvent was removed by distillation in vaccuo and the residue partioned between ethyl acetae and water. The ethyl acetate layer was dried ($MgSO_4$) and evaporated to give 13.23 g of the desilylsted benzyl alcohol tainted with a silyl fluoro- or silyloxy- side product from the cleaved protecting group. This material was assumed to contain a quantitative yield of the desired benzyl alcohol (20 mmol) and dissolved in chloroform (300 mL). The cooled solution (0°C) was treated with triethylamine (2.23 g, 3.1 mL, 22 mmol) followed by the dropwise addition of methane- sulfonyl chloride (2.29 g, 1.55 mL, 20 mmol) in chloroform (50 mL). The reaction was allowed to thaw to ambient temperature and stirred for 18 h. The reaction was washed with 5% sodium hydrogensulfate solution (2 x 150 mL) then dried and evaporated to give 10.25 g of crude product as the benzyl chloride. A portion of this material (ca. 5 g) was purified further by elution from a 400 g column of silica gel
with 3:1 hexane:ethyl acetate. The pure N-[methyl(2-(chloromethyl)phenyl)]-N-[(N'-carbo-t-butoxy)piperidin-4-yl]-(3-cyano)benzamide (3.1 g, 6.43 mmol) was isolated from the eluent as a white solid mp: 165-170°C.

1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one: The pure N-[methyl(2-(chloromethyl)phenyl)]-N-[(N'-carbo-t-butoxy)piperidin-4-yl]-(3-cyano)benzamide (3.1 g, 6.43 mmol) was dissolved in dimethylformamide (30 mL), cooled to 0°C and a 60% suspension of sodium hydride in mineral oil (0.52 g of suspension, 12.46 mmol) was added. The reaction was complete after 2h at 0°C; it was diluted with water (150 mL) and extracted with ethyl

acetate (3 x 50 mL). The ethyl acetate solution was washed with brine (5 x 50 mL), then was dried and evaporated. The yield of the cyclized product was 2.7 g (6.05 mmol); this material was contaminated with a small amount of mineral oil but was carried on to the next step without further purification.

The t-butoxycarbonyl protecting group on the product prepared above (2.7 g, 6.05 mmol) was removed by treatment with 4N hydrogen chloride in dioxane (15 mL) at $0^{o}C$ for 3 h. The reaction mixture was purged with nitrogen gas, then evaporated. The residue was dissolved in water (50 mL) and washed with ethyl ether (2 x 25 mL). The water solution was made basic (pH 12) with 10% sodium hydroxide solution and the product extracted with ethyl acetate (3 x 50 mL). The ethyl acetate solution was washed with 1N aqueous sodium hydroxide, then was dried ($MgSO_4$) and evaporated to give 1.62 g (4.68 mmol) of 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one as a tan solid, mp 115.8 ^{o}C; HRMS for $C_{21}H_{23}N_4O$ $(M+H)^+$: calc. 347.187187, found 347.184824.

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one:
A solution of 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one (0.805 g, 2.33 mmol) in tetrahydrofuran (50 mL) was cooled to $0^{o}C$ and triethylamine (0.26 g, 0.36 mL 2.6 mmol) was added. To this mixture a tetrahydrofuran solution (25 mL) of benzylsulfonyl chloride (0.5 g, 2.6 mmol) was added dropwise. The reaction mixture was allowed to thaw to ambient temperature and stirred for 24 h.TLC indicated that the reaction was complete (10% methanol in chloroform). The mixture was evaporated and the residue suspended in a 3:1 mixture of water:1N hydrogen chloride solution. The product solidified, the suspension was filtered and the resulting powder air-dried, to give 0.89 g of crude product. This material was purified further by flash chromatography with a column of silica gel (80 g) and eluting

with 2:1 then 1:1 hexane:ethyl acetate. From the eluent there was isolated 0.41 g (0.82 mmol) of pure 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one, mp: 205-207 ^{o}C.

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one: A solution of 0.41 g (0.82 mmol) of pure 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in chloroform (10 mL) was added to a saturated solution of dry, gaseous hydrogen chloride in dry methanol (10 mL) and chloroform (50 mL) at -78^{o}C. The reaction vessel was stoppered tightly and allowed to thaw to ambient temperature; this mixture was maintained in this fashion for 18 h. After this time, excess hydrogen chloride gas was removed from the reaction mixture by purging with a stream of dry nitrogen gas; the solution was then evaporated and pumped on for several hours to remove traces of free hydrogen chloride gas. The resulting imidate was detected by LRMS:m/z $(M+H)^+$ = 533. This material was dissolved in a solution of dry chloroform (20 mL) and 2.0 M ammonia in methanol (5 mL, 10 mmol), the reaction vessel was stoppered tightly and stirred at ambient temperature for 6 days. The reaction mixture was evaporated and there was obtained about 0.45 g of the amidine product contaiminated with the amide side product. This mixture was purified by HPLC, eluting with a an aqueous phase of 0.05% trifluoroacetic acid in water and an organic phase of 0.05% trifluoroacetic acid in acetonitrile. The product, 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one (0.11 g, 0.17 mmol), was isolated as the trifluoroacetic acid salt by lyophylization of the appropriate fractions; mp: 210-211^{o}C; purity > 99.5% (HPLC); HRMS: $(M+H)^+$ for $C_{28}H_{31}N_5SO_3$, calc. 518.222587, found 518.221085.

EXAMPLE 22

Preparation of 1,2,4,5-tetrahydro-2-(thiopen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one

The intermediate 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one was sulfonylated with (thiophen-2-yl)sulfonyl chloride according to the procedure outlined for the preparation of 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in EXAMPLE 21.

The title compound was obtained via the imidate according to the procedure for 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one of EXAMPLE 21 by starting with the intermediate prepared above. LRMS: m/z = 509; mp = 119-120°C.

EXAMPLE 23

Preparation of 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one

The intermediate 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one was prepared from methyl 3,4-dimethoxy-6-cyanobenzoate according to the procedure for the preparation of 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in EXAMPLE 21.

The intermediate 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one was sulfonylated with benzylsulfonyl chloride according to the procedure outlined for the preparation of 1,2,4,5-tetrahydro-2-((phenyl)methane)sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in EXAMPLE 21.

The title compound was obtained via the imidate according to the procedure for 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one of EXAMPLE 21 by starting with the intermediate prepared above. HRMS: $(M+H)^+$ for $C_{30}H_{35}N_5O_5S$, calc. 578.243716, found 578.245119.

EXAMPLE 24

Preparation of 1,2,4,5-tetrahydro-2-(thiophen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one

The intermediate 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one was prepared from methyl 3,4-dimethoxy-6-cyanobenzoate according to the procedure for the preparation of 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in EXAMPLE 21.

The intermediate 1,2,4,5-tetrahydro-2-(piperidin-4-yl)-4-(3-cyanophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one was sulfonylated with (thiophen-2-yl)sulfonyl chloride according to the procedure outlined for the preparation of 1,2,4,5-tetrahydro-2-((phenyl)methane)sulfonyl)piperidin-4-yl)-4-(3-cyanophenyl)-3H-2,4-benzodiazepin-3-one in EXAMPLE 21.

The title compound was obtained via the imidate according to the procedure for 1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one of EXAMPLE 21 by starting with the intermediate prepared above. HRMS: $(M+H)^+$ for $C_{27}H_{31}N_5O_5S_2$, calc. 570.184488, found 570.186900.

EXAMPLES 25 to 55 (shown in Table 7)

Examples 25 to 55 were prepared by essentially the same preparative methods as described above for Example 8; the only changes involved the sulfonylation, alkylation or acylation of the common intermediate N-(3-cyanophenyl)-N'-(piperidin-4-

yl)cycloheptylurea. In each case, the same procedure using the appropriate sulfonyl chloride, sulfamoyl chloride, alkyl chloride or acyl chloride in tetrahydrofuran with triethylamine was used. Following imidate formation, the reaction with methanolic ammonia to give the amidine product was executed as described in Example 13.

An exceptional case was the preparation of Example 28; this product was obtained as a by-product of the formation of the amidine Example 29. During the methanolic ammonia step competing deacylation of Example 29 led to the formation of Example 28. Both Examples 28 and 29 were obtained pure and homogeneous by HPLC purification of the mixture obtained during amidine formation under standard preparative HPLC purification conditions.

EXAMPLE 56

Preparation of N-(3-amidinophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea

The title compound was prepared from N-(3-cyanophenyl)-N'-(1-((phenyl)methane)sulfonyl)piperidin-4-yl)cycloheptylurea found in Example 8

N-(3-cyanophenyl)-N'-(1-((phenyl)methane)sulfonyl)piperidin-4-yl)cycloheptylurea (1.94 g, 4.29 mmol) in dimethylformamide (25 mL) was cooled to -10^{o}C and 1M potassium t-butoxide solution in tetrahydrofuran (12.9 mL, 12.9 mmol) was added dropwise. The reaction was stirred for 15 min at -10^{o}C then methyl iodide (1.83 g, 12.9 mmol) was added. After 2 h reaction was complete by TLC; the reaction micture was poured into water (200 mL), then was extracted with ethyl acetate (3 x 50 mL). The ethyl acetate extracts were washed with water (5 x 50 mL), dried ($MgSO_4$) and evaporated to give 0.55 g of N-(3-cyanophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)-sulfonyl)-piperidin-4-yl)cycloheptylurea; LRMS $(M + NH_4)^+$ m/z = 498.

To 0.55 g of N-(3-cyanophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)-sulfonyl)-piperidin-4-yl)cycloheptylurea

(1.14 mmol) in pyridine (20 mL) with triethylamine (1 mL) was passed a stream of gaseous hydrogen sulfide for 30 min. The reaction mixture was stoppered tightly and allowed to stand for 18 h. The solution was then poured into 1N hydrochloric acid solution (250 mL) and extracted with ethyl acetate (3 x 50 mL). The ethyl acetate solution was dried and evaportated to give 0.53 g (1.03 mmol) of N-(3-thioamidophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)-sulfonyl)-piperidin-4-yl)cycloheptylurea; LRMS $(M + H)^+$ m/z = 515.

The product prepared above, 0.53 g (1.03 mmol) of N-(3-thioamidophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)-sulfonyl)-piperidin-4-yl)cycloheptylurea, was stirred in methyl iodide (10 mL) for 2 h. The reaction was then evaporated to give 0.62 g (1.03 mmol) of the thioimidate.

The thioimidate (o.62 g, 1.03 mmol) was stirred with ammonium acetate (0.45g, 5.9 mmol) in methanol (20 mL) and heated at 60°C for 2 h. The reaction was then evaporated, the residue stirred in dichloromethane, the insoluable material removed by filtration and the dichloromethane solution evaporated to give ca. 0.5 g of crude amidine. This material was purified by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) to give 0.143 g of the title compound following lyophylization of the appropriate fractions; HRMS $(M+H)^+$ calc. 489.253887, found 498.252412.

EXAMPLE 57

Preparation of N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)carbamide)morpholin-3-yl))cycloheptylurea

N-benzyl 3-(aminomethyl)morpholine: N-benzyl 3-(chloro-methyl)morpholine (10g, 44.3 mmol) in dimethylformamide (200 mL) with sodium azide (8.64 g, 133 mmol) and potassium iodide (0.73 g) was heated at 100°C for 72 h. The reaction was poured into water (1 L) and extracted with ethyl acetate (3 x 150 mL). The ethyl acetate layer was washed with water (5 x

150 mL), then dried ($MgSO_4$) and evaporated to give 9.28 g of material. This was purified further by flash chromatography using 3:1 hexane:ethyl acetate as the eluent. There was obtained 7.89 g of the pure azide.

The material prepared above was dissolved in methanol (300 mL) and palladium hydroxide catalyst (1.0 g) was added. This mixture was stirred under an atmosphere of hydrogen gas at ambient pressure for 2 h, whereupon selective reduction of the azide group was complete. The reaction mixture was purged with nitrogen gas and the catalyst removed by filtration through a Celite pad.After removal of the solvent there was obtained 5.80 g of N-benzyl 3-(aminomethyl)morpholine (28.1 mmol); LRMS $(M+H)^+$ m/z = 207.

N-(3-cyanophenyl)-N'-(methyl(N-methyl(phenyl))morpholin-3-yl))cycloheptylurea: A mixture of 5.80 g of N-benzyl 3-(aminomethyl)morpholine (28.1 mmol) and 3-cyanophenyl isocyanate (4.46 g, 31 mmol) in dimethylformamide (100 mL) was stirred at ambient temperature for 18 h. The reaction was diluted with water (500 mL) then extracted with ethyl acetate (3 x 100 mL). The ethyl acetate solution was washed with water (5 x 100 mL), dried ($MgSO_4$) and evaporated to give 9.49 g of the urea (27.1 mmol); LRMS $(M+H)^+$ m/z = 351.

To a mixture of sodium hydride (3.25 g of a 60% suspension in mineral oil, 81.3 mmol) in dimethylformamide (450 mL) was added dropwise 9.49 g of the urea (27.1 mmol) prepared above as a solution in dimethylformamide (50 mL). This mixture was stirred for 30 min, then 1,71 g of 1,4-dibromobutane (54.2 mmol) in dimethylformamide (40 mL) was added slowly. The reaction was heated to 70°C for 6 h then poured into water (2 L) and extracted with ethyl acetate (3 x 250 mL). The ethyl acetate extract was washed with water (5 x 250 mL) , was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using 2:1 hexane:ethyl acetate as an eluent. There was obtained 7.59 g of N-(3-cyanophenyl)-N'-(methyl(N-

methyl(phenyl))morpholin-3-yl))cycloheptylurea; LRMS $(M+H)^+$ m/z = 405.

N-(3-cyanophenyl)-N'-(methyl(morpholin-3-yl))cycloheptylurea: To N-(3-cyanophenyl)-N'-(methyl(N-methyl(phenyl))morpholin-3-yl))cycloheptylurea (4.66 g, 11.55 mmol) in dichloromethane (100 mL) was added 1-chloroethyl chloroformate (1.81 g, 12.7 mmol) in dichloromethane (10 mL). After 2 h the reaction was complete by TLC; the solvent was removed by evaporation in vaccuo and replaced by methanol (60 mL). The mixture was refluxed for 1 h then the solvent evaporated to give 3.53 g of N-(3-cyanophenyl)-N'-(methyl(morpholin-3-yl))cycloheptyl-urea; LRMS $(M+H)^+$ m/z = 315.

N-(3-cyanophenyl)-N'-(methyl((phenylmethane)carbamide)-morpholin-3-yl))cycloheptylurea: To 1.0 g of N-(3-cyanophenyl)-N'-(methyl(morpholin-3-yl))cycloheptylurea (3.18 mmol) in tetrahydrofuran (30 mL) with triethylamine (0.68 g, 6.7 mmol) at 0°C was added phenylacetyl chloride (0.54 g, 3.5 mmol) in tetrahydrofuran (10 mL). The mixture was allowed to thaw to ambient temperature and stirred for 18 h. After this time, the solvent was removed by evaporation in vaccuo and the residue purified by flash chromatography with 10% methanol in chloroform used as the eluent. There was obtained 1.17 g (2.7 mmol) of N-(3-cyanophenyl)-N'-(methyl((phenyl-methane)carbamide)morpholin-3-yl))cycloheptylurea as product; LRMS $(M+H)^+$ m/z = 433.

N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)carbamide)-morpholin-3-yl))cycloheptylurea: To a saturated solution of gaseous hydrogen chloride in dry chloroform (20 mL) and dry methanol (8 mL) at -78°C was added dropwise a chloroform (5 mL) solution of 1.17 g (2.7 mmol) of N-(3-cyanophenyl)-N'-(methyl((phenyl-methane)carbamide)morpholin-3-yl))cycloheptylurea. This mixture was stoppered tightly, was allowed to thaw to ambient temperature and was stirred for 18 h. The solvent was removed in vaccuo to give 1.04 g of the corresponding imidate; LRMS $(M+H)^+$ m/z = 465.

The imidate prepared above was dissolved in 2M ammonia in methanol solution (6.72 mmol, 3.36 mL), the flask was stoppered securely and the mixture stirred at ambient temperature for 18 h. After this time the solvent was removed in vaccuo and the residue (ca. 1.2 g) was purified by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) to give 0.12 g of N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)carbamide)-morpholin-3-yl))cycloheptylurea; mp 49-53 ^{O}C; HRMS $(M+H)^+$: calc. 450.250515, found 450.251817.

EXAMPLE 58

Preparation of N-(3-amidinophenyl)-N'-(methyl((thiophen-2-yl)sulfonyl)morpholin-3-yl))cycloheptylurea

This compound was prepared by the same methods used for Example 57. Starting with the common intermediate N-(3-cyanophenyl)-N'-(methyl(morpholin-3-yl))cycloheptylurea, this material was sulfonylated with (thiophen-2-yl)sulfonyl chloride using the same conditions for the acylation described above. There was obtained 0.75 g of the sulfonylation product following purification by flash chromatography using a gradient of 2:1 hexane:ethyl acetate to 1:2 hexane:ethyl acetate as a gradient; LRMS $(M+H)^+$ m/z = 461.

The imidate and subsequently, the amidine N-(3-amidinophenyl)-N'-(methyl((thiophen-2-yl)sulfonyl)morpholin-3-yl))cycloheptylurea were obtained as described. Following HPLC purification 0.32 g of the title compound was isolated; mp 78-83 ^{O}C; HRMS $(M+H)^+$: calc. 478.158273, found 478.156983.

EXAMPLE 59

Preparation of N-(3-amidinophenyl)-N'-(methyl((phenylmethane)sulfonyl)morpholin-3-yl))cycloheptylurea

This compound was prepared by the same methods used for Example 57. Starting with the common intermediate N-(3-cyanophenyl)-N'-(methyl(morpholin-3-yl))cycloheptylurea, this material was sulfonylated with (phenyl)methylsulfonyl chloride using the same conditions for the acylation described above. There was obtained 0.68 g of the sulfonylation product following purification by flash chromatography using a gradient of 1:1 hexane:ethyl acetate to 1:3 hexane:ethyl acetate as a gradient; LRMS $(M+H)^+$ m/z = 469.

The imidate and subsequently, the amidine N-(3-amidinophenyl)-N'-(methyl((phenylmethane)sulfonyl)morpholin-3-yl))cycloheptylurea were obtained as described above. Following HPLC purification 0.102 g of the title compound was isolated; mp 45-53 ^{o}C; HRMS $(M+H)^+$: calc. 486.217502, found 486.217928.

EXAMPLE 60

Preparation of N-(3-amidinophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptylurea

N-Benzyl 3-aminopiperidine: To 10.0 g of N-benzyl 3-hydroxypiperidine hydrogen chloride salt (44 mmol) in chloroform (200 mL) with triethylamine (9.34 g, 92.4 mmol) at 0^{o}C was added dropwise methanesulfonyl chloride (5.54 g, 48.4 mmol) in chloroform (10 mL).The reaction mixture was allowed to thaw to ambient temperature and stirred 72 h. After this time, the solvent was removed in vaccuo, the residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL). The organic solution was dried ($MgSO_4$) and evaporated to give 9.1 g (33.8 mmol) of the mesitylate.

The material prepared above was dissolved in dimethylformamide (200 mL) and stirred at 100 °C with sodium azide (11 g, 170 mmol). After 48 h the reaction was complete by TLC; it was diluted with brine (200 mL) and extracted with ethyl acetate (3 x 100 mL). The ethyl acetate extracts were washed with water (5 x 100 mL), then dried and evaporated to give 6.12 g of the azide; LRMS $(M+H)^+$ m/z = 217.

The azide (6.12 g, 28.4 mmol) in methanol (250 mL) with palladium hydroxide catalyst (1.0 g) was stirred under an atmosphere of hydrogen gas at ambient pressure for 1 h 15 min. After this time selective reduction of the azide was complete. The reaction mixture was purged with nitrogen gas and the catalyst removed by filtration through a Celite pad. The solvent was removed by distillation in vaccuo to give 4.3 g of N-benzyl 3-aminopiperidine; LRMS $(M+H)^+$ m/z = 191.

N-(3-cyanophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptyl-urea: A mixture of 4.3 g of N-benzyl 3-aminopiperidine (22.6 mmol) and 3-cyanophenyl isocyanate (3.58 g, 24.9 mmol) in dimethylformamide (100 mL) was stirred at ambient temperature for 18 h. The reaction was diluted with water (500 mL) and extracted with ethyl acetate (3 x 150 mL). The organic solution was washed with water (5 x 100 mL), dried and evaporated. This material was purified further by flash chromatography on silica gel using a gradient of 1:1 to 3:1 ethyl acetate:hexane. There was obtained 3.18 g of the pure urea (9.52 mmol); LRMS $(M+H)^+$ m/z = 335.

To 1.14 g of sodium hydride (60% suspension, 28.6 mmol) in dimethylformamide (160 mL) was added a dimethylformamide (20 mL) solution of the urea (3.18 g, 9.52 mmol). After 30 min, 1,4-dibromobutane (4.32 g, 20 mmol) in dimethylformamide (10 mL) was added dropwise, then the mixture was heated to 70 °C for 3 h. The reaction was diluted with water (700 mL) and extracted with ethyl acetate (3 x 100 mL). The organic solution was washed with water (5 x 100 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography

on silica gel using an elution gradient of 5 to 10% methanol in chloroform. There was obtaine 3.17 g of N-(3-cyanophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptyl-urea; LRMS $(M+H)^+$ m/z = 389.

N-(3-amidinophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptyl-urea: To a saturated solution of hydrogen chloride gas in dry methanol (8 mL) and dry chloroform (15 mL) at -78 ^{O}C was added a chloroform (5 mL) solution of N-(3-cyanophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptyl-urea (0.5 g, 1.29 mmol). The reaction mixture was stoppered securely and allowed to stir at ambient temperature for 18 h. After this time the solvent was removed in vaccuo and 0.49 g of the imidate hydrochloride salt was obtained; LRMS $(M+H)^+$ m/z = 422.

The imidate obtained above was dissolved in 2<u>M</u> ammonia in methanol (1.75 mL, 3.5 mmol). The reaction vessel was stoppered securely and the mixture stirred at ambient temperature for 18 h. After this time the solvent was removed in vaccuo and the residue was purified by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) to give 0.015 g of pure N-(3-amidinophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptylurea; HRMS $(M+H)^+$: calc.406.260686, found 406.259064.

EXAMPLE 61

Preparation of N-(3-amidinophenyl)-N'-((N-(benzyl)sulfonyl)-piperidin-3-yl)cycloheptylurea

N-(3-cyanophenyl)-N'-(piperidin-3-yl)cycloheptylurea: A mixture of N-(3-cyanophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptyl-urea (prepared in Example 60, 2.7 g, 6.98 mmol) and α-chloroethyl chloroformate (1.09 g, 7.65 mmol) was stirred at ambient temperature for 2.5 h, whereupon the reaction was complete as judged by TLC.The solvent was removed by evaporation in vaccuo and was replaced with methanol (40 mL). The reaction was heated at reflux until all of the newly

formed intermediate was consumed as indicated by TLC. Evaporation of the solvent gave 2.49 g of N-(3-cyanophenyl)-N'-(piperidin-3-yl)cycloheptylurea; LRMS $(M+H)^+$ m/z = 299.

N-(3-cyanophenyl)-N'-((N-(benzyl)sulfonyl)piperidin-3-yl)cycloheptylurea: To N-(3-cyanophenyl)-N'-(piperidin-3-yl)cycloheptylurea (1.2 g, 4.03 mmol) and triethylamine (0.85 g, 8.46 mmol) in tetrahydrofuran (30 mL) at 0 ^{o}C was added benzylsulfonyl chloride (0.92 g, 4.83 mmol) in tetrahydrofuran solution (10 mL). The reaction was allowed to thaw to ambient temperature then stirred for 18 h. The reaction mixture was evaporated and the residue was dissolved in ethyl acetate (100 mL). The organic solution was washed with 1N sodium hydroxide solution (100 mL), 1N hydrochloric acid (100 mL) and saturated sodium hydrogen carbonate (100 mL). The solution was dried ($MgSO_4$) and evaporated to give 0.99 g (2.19 mmol) of N-(3-cyanophenyl)-N'-((N-(benzyl)-sulfonyl)piperidin-3-yl)cycloheptylurea; LRMS $(M+H)^+$ m/z = 453.

N-(3-amidinophenyl)-N'-((N-(benzyl)sulfonyl)piperidin-3-yl)cycloheptylurea: To a -78 ^{o}C saturated solution of hydrogen chloride gas in dry chloroform (20 mL) and methanol(10 mL) was added 0.99 g (2.19 mmol) of N-(3-cyanophenyl)-N'-((N-(benzyl)-sulfonyl)piperidin-3-yl)cycloheptylurea in chloroform (5 mL). The reaction vessel was stoppered securely, was allowed to thaw to ambient temperature and was stirred 18 h. After this time the solvent was removed by evaporation in vaccuo and there was obtained 1.04 g of the imidate as the hydrogen chloride salt; LRMS $(M+H)^+$ m/z = 485.

The imidate prepared above was dissolved in 2M ammonia in methanol solution (3.22 mL, 6.44 mmol). The reaction was stoppered securely and was stirred for 18 h. Following removal of the solvent and purification by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) there was obtained 0.316 g of N-(3-amidinophenyl)-N'-((N-(benzyl)-

sulfonyl)piperidin-3-yl)cycloheptylurea; HRMS $(M+H)^+$: calc.470.225587, found 470.221857.

Additionally, there was isolated as a slower eluting peak 0.066 g of the amide side product, N-(3-amidophenyl)-N'-((N-(benzyl)sulfonyl)piperidin-3-yl)cycloheptylurea.

EXAMPLE 62

Preparation of N-(3-amidinophenyl)-N'-((N-(thiophen-2-yl)sulfonyl)piperidin-3-yl)cycloheptylurea

This compound was prepared by the same methods used for Example 61. Starting with the common intermediate N-(3-cyanophenyl)-N'-(piperidin-3-yl)cycloheptylurea, this material was sulfonylated with (thiophen-2-yl)sulfonyl chloride using the same conditions for the sulfonylation described above. There was obtained 0.87 g of the sulfonylation product following purification by flash chromatography using a gradient of 2:1 hexane:ethyl acetate to 1:1 hexane:ethyl acetate as a gradient; LRMS $(M+H)^+$ m/z = 445.

The imidate and subsequently, the amidine N-(3-amidinophenyl)-N'-((N-(thiophen-2-yl)sulfonyl)piperidin-3-yl)cycloheptylurea were obtained as described above. Following HPLC purification 0.234 g of the title compound was isolated; HRMS $(M+H)^+$: calc. 462.163359, found 462.164841.

Additionally, there was isolated as a slower eluting peak 0.045 g of the amide side product, N-(3-amidophenyl)-N'-((N-(thiophen-2-yl)sulfonyl)piperidin-3-yl)cycloheptylurea ; HRMS $(M+H)^+$: calc. 463.147374, found 463.146300.

EXAMPLE 63

Preparation of N-(3-amidinophenyl)-N'-(4-(2-sulfonamido-phenyl)phenyl)cycloheptylurea

N-(3-cyanophenyl)-N'-(4-bromophenyl)cycloheptylurea: A mixture of 3-cyanophenyl isocyanate (3.76 g, 26.1 mmol) and 4-bromoaniline (4.5 g, 26.1 mmol) in 1:1 tetrahydrofuran:chloroform (100 mL). After 72 h at ambient temperature, product was isolated by filtration, the filtrate was washed with cold chloroform and air dried to give 6.6 g of N-(3-cyanophenyl)-N'-(4-bromophenyl)urea (21 mmol).

To 1.41 g of sodium hydride (60% suspension, 33.6 mmol) in dimethylformamide (300 mL) was added a dimethylformamide (20 mL) solution of 6.6 g of N-(3-cyanophenyl)-N'-(4-bromophenyl)urea (21 mmol). After 30 min, 1,4-dibromobutane (6.2 g, 28.6 mmol) in dimethylformamide (10 mL) was added dropwise, then the mixture was heated to 60 ^{o}C for 2 h and then was stirred at ambient temperature for 18 h. The reaction was diluted with water (700 mL) and extracted with ethyl acetate (3 x 100 mL). The organic solution was washed with water (5 x 100 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel using an elution gradient of 5 to 10% methanol in chloroform. There was obtained 3.68 g of N-(3-cyanophenyl)-N'-(4-bromophenyl)cycloheptylurea.

N-(3-cyanophenyl)-N'-(4-(2-((N-t-butyl)sulfonamido)phenyl)-phenyl)cycloheptylurea: A mixture of N-(3-cyanophenyl)-N'-(4-bromophenyl)cycloheptylurea (4.0 g, 10.81 mmol), 2-((N-t-butyl)sulfonamido)phenylboronic acid (3.9 g, 15.2 mmol), tetrabutylammonium bromide (0.203 g) and sodium carbonate (2.47 g) in benzene (170 mL) was thoroughly purged with dry nitrogen gas. Tetrakis(triphenylphosphine)palladium(0) catalyst (0.635 g) was added and the mixture was heated at reflux under a nitrogen atmosphere for 18 h. The benzene solution was washed with water (3 x 100 mL) and brine (100 mL), then dried ($MgSO_4$) and evaporated. The crude product was

triturated with n-butylchloride, filtered and air dried to give 3.92 g of N-(3-cyanophenyl)-N'-(4-(2-((N-t-butyl)sulfon-amido)phenyl)-phenyl)cycloheptylurea.

N-(3-amidinophenyl)-N'-(4-(2-sulfonamidophenyl)phenyl)-cycloheptylurea: A solution of 3.0 g of N-(3-cyanophenyl)-N'-(4-(2-((N-t-butyl)sulfon-amido)phenyl)phenyl)cycloheptyl-urea (5.98 mmol) in dry methanol (40 mL) and dry chloroform (300 mL) was saturated with hydrogen chloride gas with ice cooling. This solution was stoppered tightly and was stirred for 18 h at ambient temperature. The solvent was removed by evaporation and the residue dissolved in 2M ammonia in methanol (60 mmol, 30 mL). This solution was stirred in a securely stoppered reaction vessel for 48 h at ambient temperature. After this time the solvent was removed in vaccuo and 2.28 g of crude product was obtained. A portion (0.735 g) of this material was purified by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) to give 0.396 g of pure N-(3-amidinophenyl)-N'-(4-(2-sulfonamidophenyl)-phenyl)cycloheptylurea ; mp 163-166 °C HRMS $(M+H)^+$: calc.464.175637, found 464.177525.

EXAMPLE 64

Preparation of N-(3-amidinophenyl)-N'-(5-(2-sulfonamido-phenyl)pyridin-2-yl)cycloheptylurea

Example 64 was prepared by a procedure similar to that used for Example 63 with the exception that 2-amino-5-bromopyridine was substituted for 4-bromoaniline in the intial step. There was obtained 0.043 g of N-(3-amidinophenyl)-N'-(5-(2-sulfonamido-phenyl)pyridin-2-yl)cycloheptylurea as a bis trifluoroacetate salt; mp 75-79 °C; HRMS $(M+H)^+$: calc. 465.170886, found 465.170759.

EXAMPLE 65

Preparation of N-(3-amidinophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)phenyl))cycloheptylurea

N-(3-cyanophenyl)-N'-(methyl(4-bromo)phenyl)urea: A mixture of 4-bromobenzyl amine (3.81 g, 20 mmol) and 3-cyanophenyl isocyanate (2.65 g, 18.4 mmol) in dimethylformamide (60 mL) was stirred at ambient temperature for 48 h. The reaction was partioned between 1N hydrochloric acid solution (200 mL) and ethyl acetate (200 mL). The ethyl acetate solution was washed with water (5 x 100 mL), then dried ($MgSO_4$) and evaporated to give 5.33 g of N-(3-cyanophenyl)-N'-(methyl(4-bromo)phenyl)urea.

N-(3-cyanophenyl)-N'-(methyl(4-bromophenyl))cycloheptyl-urea: To 1.82 g of sodium hydride (60% suspension, 45.3 mmol) in dimethylformamide (270 mL) was added a dimethylformamide (30 mL) solution of the N-(3-cyanophenyl)-N'-(methyl(4-bromo)phenyl)urea (4.98 g g, 15.1 mmol). After 30 min, 1,4-dibromobutane (6.52 g, 30.2 mmol) in dimethylformamide (10 mL) was added dropwise, This mixture was heated to 70 °C for 3 h then cooled to ambient temperature and stirred for 48 h. The reaction was diluted with water (1 L) and extracted with ethyl acetate (4 x 250 mL). The organic solution was washed with water (5 x 150 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with 1% methanol in chloroform. There was obtained 2.3 g of N-(3-cyanophenyl)-N'-(methyl(4-bromophenyl))cycloheptylurea.

N-(3-cyanophenyl)-N'-(methyl(4-(2-(N-t-buty)sulfonamido-phenyl)phenyl))cycloheptylurea: A mixture of N-(3-cyanophenyl)-N'-(methyl(4-bromophenyl))cycloheptylurea (1.24 g, 3.2 mmol), 2-((N-t-butyl)sulfonamido)phenylboronic acid (1.17 g, 4.5 mmol), tetrabutylammonium bromide (0.06 g) and sodium carbonate (0.73 g) in benzene (50 mL) and water (5 mL) was thoroughly purged with dry nitrogen gas. Tetrakis(tri-phenylphosphine)palladium(0) catalyst (0.188 g) was added and the mixture was heated at reflux under a nitrogen atmosphere

for 18 h. The benzene solution was washed with water (3 x 100 mL) and brine (100 mL), then dried ($MgSO_4$) and evaporated to give 2.0 g of crude product. Recrystallization from acetone gave 0.80 g of N-(3-cyanophenyl)-N'-(methyl(4-(2-(N-t-buty)sulfonamido-phenyl)phenyl))cycloheptylurea; mp 177-179 ^oC.

An additional 0.365 g of product was recovered from the mother liquors by silica gel chromatography using 1% methanol in chloroform as an eluent.

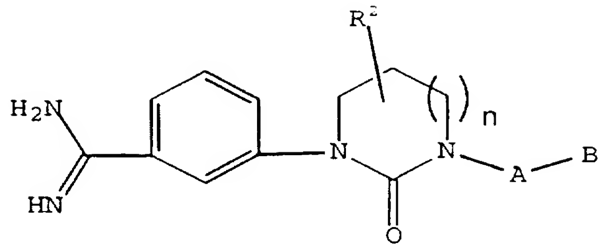
N-(3-cyanophenyl)-N'-(methyl(4-(2-sulfonamido-phenyl)phenyl))cycloheptylurea: A solution of 1.17 g of N-(3-cyano-phenyl)-N'-(methyl(4-(2-(N-t-buty)sulfonamido-phenyl)phenyl))cycloheptylurea (2.27 mmol) in trifluoroacetic acid (30 mL) was heated at reflux for 1 h. The reaction was evaporated and the residue suspended in 10% sodium hydroxide solution (30 mL). The suspension was extracted with ethyl acetate (50 mL), the extracts were washed with 10% sodium hydroxide solution (2 x 25 mL) and brine (25 mL). The solution was dried ($MgSO_4$) and evaporated to give 0.72 g of crude product. This material was purified by column chromatography using a gradient of 1.5 to 2.5% methanol in chloroform. There was obtained 0.55 g of N-(3-cyanophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)phenyl))cycloheptylurea.

N-(3-amidinophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)-phenyl))cycloheptylurea: A solution of 0.55 g of N-(3-cyanophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)-phenyl))cycloheptylurea (1.2 mmol) in dry methyl acetate (70 mL) and dry methanol (0.192 g, 0.24 mL, 6.0 mmol) was cooled to 0 ^oC and saturated with dry hydrogen chloride gas.The reaction was stoppered tightly and stirred at ambient temperature 18 h. Precipitation of the imidate product was initiated by the addition of ethyl ether (70 mL) to the cold solution. The solid was isolated by filtration and maintained in vaccuo for 18 h to remove the last traces of hydrogen

chloride gas; there was obtained 0.50 g of the imidate as the hydrogen chloride salt.

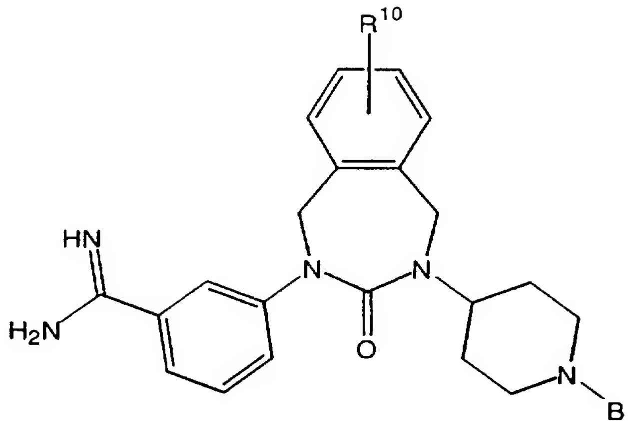
The imidate from above was stirred for 18 h in a methanol (20 mL) solution of ammonium acetate (0.462 g , 6 mmol). The reaction was evaporated and partioned between ethyl acetate (50 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate solution was dried and evaporated to give 0.16 g of the amide side-product. Lyophylization of the hydrochloric acid solution gave 0.39 g of the crude amidine. Purification of this material by HPLC (gradient elution with a mixture of 0.05% aqueous trifluoroacetic acid and 0.05% trifluoroacetic acid in acetonitrile) gave 0.258 g of N-(3-amidinophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)phenyl))cycloheptylurea as the trifluoroacetic acid salt; mp 90-94 ^{o}C; HRMS $(M+H)^{+}$ calc. 478.191671, found 478.191287.

Table 5



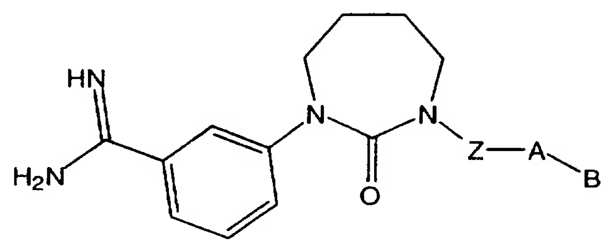
Ex	n	R^2	A	B	HRMS $(M+H)^+$ m/z
1	0	H	4-piperidinyl	N-benzyl	378.229774
2	1	H	4-piperidinyl	N-benzyl	LRMS $(M+H)^+$ m/z 392
3	2	H	phenyl	4-amidino	351.1936
4	2	H	benzyl	4-amidino	365.209496
5	2	H	4-piperidinyl	N-(amidino)	358.2349
6	2	H	4-piperidinyl	N-benzyl	LRMS $(M+H)^+$ m/z 406
7	2	H	4-piperidinyl	N-(1-phenethyl))	420.276129
8	2	H	4-piperidinyl	N-benzylsulfonyl	470.219813
9	2	H	4-piperidinyl	N-benzoyl	421.222804
10	2	H	4-piperidinyl	N-benzylcarbonyl	434.255065
11	2	H	4-piperidinyl	N-phenylsulfonyl	456.204189
12	2	H	4-piperidinyl	N-(4-acetamido-phenylsulfonyl)	513.226577
13	2	H	4-piperidinyl	N-(2-amino-phenylsulfonyl)	471.218097
14	2	H	4-piperidinyl	N-(3-amino-phenylsulfonyl)	471.219532
15	2	H	4-piperidinyl	N-(4-amino-phenylsulfonyl)	471.217059
16	2	H	4-piperidinyl	N-(2-aminophenyl-methane-sulfonyl)	485.235037
17	2	H	4-piperidinyl	N-(2-acetamido-phenylmethane-sulfonyl)	527.246420
18	0	$-CH=CH_2$	4-piperidinyl	N-phenylmethane-carbonyl	418.223792
19	0	$-CH=CH_2$	4-piperidinyl	N-benzylsulfonyl	468.204978
20	0	$-CH=CH_2$	4-piperidinyl	N-phenylsulfonyl	454.191418

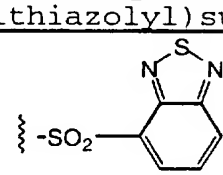
Table 6



Ex.	R^{10}	B	HRMS $(M+H)^+$ m/z
21	H	benzylsulfonyl	518.221085
22	H	2-thiophenylsulfonyl	LRMS: m/z = 509
23	7,8-di-OCH_3	benzylsulfonyl	578.245119
24	7,8-di-OCH_3	2-thiophenylsulfonyl	570.186900

Table 7

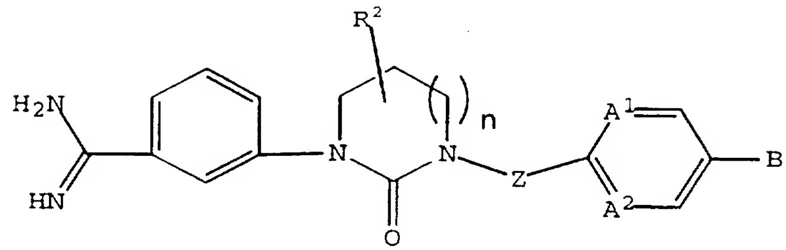


Ex.	Z-A	B*	HRMS $(M+H)^+$ m/z
25	4-piperidinyl	2-fluorophenylsulfonyl	474.198031
26	4-piperidinyl	isopropylsulfonyl	422.222957
27	4-piperidinyl	8-quinolinylsulfonyl	507.217649
28	4-piperidinyl	1-(5-amino-4-methylthiazolyl)sulfonyl	492.183742
29	4-piperidinyl	1-(5-N-acetylamino-4-methylthiazolyl)sulfonyl	534.193475
30	4-piperidinyl		514.168829
31	4-piperidinyl	2-(5-chlorothiophenyl	497.124056

32	4-piperidinyl	3-(2-carbomethoxy) thiophenylsulfonyl	520.168929
33	4-piperidinyl	2-thiophenylsulfonyl	462.163248
34	4-piperidinyl	2-carbomethoxyphenyl-sulfonyl	514.212199
35	4-piperidinyl	2-pyridylmethyl	407.258632
36	4-piperidinyl	3-pyridylmethyl	407.255034
37	4-piperidinyl	cyclohexylaminosulfonyl	477.2646
38	4-piperidinyl	isopropylaminosulfonyl	437.2339
39	4-piperidinyl	phenylaminosulfonyl	471.2182
40	4-piperidinyl	phenylaminocarbonyl	435.2519
41	4-piperidinyl	cyclohexylaminocarbonyl	441.2968
42	4-piperidinyl	phenyl-N-methylaminosulfonyl	485.2340
43	4-piperidinyl	4-pyridylmethyl	407.255561
44	4-piperidinyl	3-pyridylmethylsulfonyl	471.218739
45	4-piperidinyl	1-naphthylsulfonyl	506.222676
46	4-piperidinyl	2-naphthylsulfonyl	506.221512
47	4-piperidinyl	5-(2-phenylsulfonyl-thiophenyl)sulfonyl	602.158636
48	4-piperidinyl	3-pyridylsulfonyl	457.204869
49	4-piperidinyl	2-(4-phenylsulfonyl-thiophenyl)sulfonyl	602.157432
50	4-piperidinyl	5-(N-methylimidazolyl) sulfonyl	460.213785
51	4-piperidinyl	2-pyridylmethylsulfonyl	471.219270
52	4-piperidinyl	2-thiophenylmethyl	412.216008
53	4-piperidinyl	4-fluorophenylsulfonyl	474.199222
54	4-piperidinyl	4-fluorophenylmethyl-sulfonyl	488.210708
53	4-piperidinyl	3,5-bistrifluoromethyl-phenylsulfonyl	592.181914
54	4-piperidinyl	2-trifluoromethylphenyl-sulfonyl	524.193512
55	4-piperidinyl	2-pyridylsulfonyl	457.202166
56	4-piperidinyl	(1,1-dimethyl-1-phenyl)methylsulfonyl	498.252412
57	3-morpholinyl-methyl	N-(benzylcarbonyl)	450.251817
58	3-morpholinyl-methyl	N-(thiophen-2-ylsulfonyl)	478.156983
59	3-morpholinyl-methyl	N-(benzylsulfonyl)	486.217928
60	3-piperidinyl	N-benzyl	406.259064
61	3-piperidinyl	N-(benzylsulfonyl)	470.221857
62	3-piperidinyl	N-(thiophenylsulfonyl)	462.164841
63	phenyl	2-sulfonamidophenyl	464.177525
64	2-pyridyl	2-sulfonamidophenyl	465.170759
65	benzyl	2-sulfonamidophenyl	478.191287

*Unless otherwise indicated, group **B** is substituted on **A** para to **Z**, if present, and the cyclourea.

Table 8



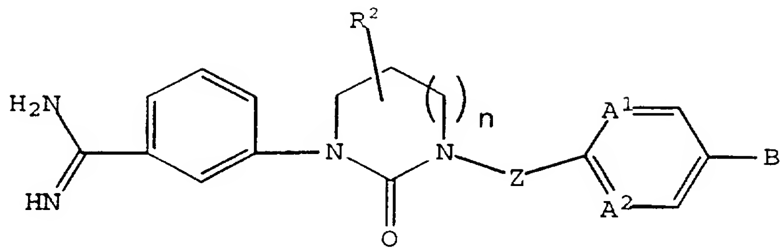
Ex.	n	R^2	Z	A^1	A^2	B
101	0	H	bond	CH	CH	amino
102	0	H	bond	CH	CH	amidino
103	0	H	bond	CH	CH	guanidino
104	0	H	bond	CH	CH	2-sulfamidophenyl
105	0	H	bond	CH	CH	2-trifluoromethylphenyl
106	0	OH	bond	CH	CH	amino
107	0	OH	bond	CH	CH	amidino
108	0	OH	bond	CH	CH	guanidino
109	0	OH	bond	CH	CH	2-sulfamidophenyl
110	0	OH	bond	CH	CH	2-trifluoromethylphenyl
111	0	$NHC(O)CH_3$	bond	CH	CH	amino
112	0	$NHC(O)CH_3$	bond	CH	CH	amidino
113	0	$NHC(O)CH_3$	bond	CH	CH	guanidino
114	0	$NHC(O)CH_3$	bond	CH	CH	2-sulfamidophenyl
115	0	$NHC(O)CH_3$	bond	CH	CH	2-trifluoromethylphenyl
116	0	$NHSO_2CH_3$	bond	CH	CH	amino
117	0	$NHSO_2CH_3$	bond	CH	CH	amidino
118	0	$NHSO_2CH_3$	bond	CH	CH	guanidino
119	0	$NHSO_2CH_3$	bond	CH	CH	2-sulfamidophenyl
120	0	$NHSO_2CH_3$	bond	CH	CH	2-trifluoromethylphenyl
121	0	OCH_3	bond	CH	CH	amino
122	0	OCH_3	bond	CH	CH	amidino
123	0	OCH_3	bond	CH	CH	guanidino
124	0	OCH_3	bond	CH	CH	2-sulfamidophenyl
125	0	OCH_3	bond	CH	CH	2-trifluoromethylphenyl
126	0	$OCH_2C_6H_5$	bond	CH	CH	amino
127	0	$OCH_2C_6H_5$	bond	CH	CH	amidino
128	0	$OCH_2C_6H_5$	bond	CH	CH	guanidino
129	0	$OCH_2C_6H_5$	bond	CH	CH	2-sulfamidophenyl
130	0	$OCH_2C_6H_5$	bond	CH	CH	2-trifluoromethylphenyl
131	0	H	CH_2	CH	CH	amino
132	0	H	CH_2	CH	CH	amidino
133	0	H	CH_2	CH	CH	guanidino
134	0	H	CH_2	CH	CH	2-sulfamidophenyl
135	0	H	CH_2	CH	CH	2-trifluoromethylphenyl
136	0	OH	CH_2	CH	CH	amino
137	0	OH	CH_2	CH	CH	amidino
138	0	OH	CH_2	CH	CH	guanidino
139	0	OH	CH_2	CH	CH	2-sulfamidophenyl
140	0	OH	CH_2	CH	CH	2-trifluoromethylphenyl
141	0	$NHC(O)CH_3$	CH_2	CH	CH	amino

142	0	NHC(O)CH_3	CH_2	CH	CH	amidino
143	0	NHC(O)CH_3	CH_2	CH	CH	guanidino
144	0	NHC(O)CH_3	CH_2	CH	CH	2-sulfamidophenyl
145	0	NHC(O)CH_3	CH_2	CH	CH	2-trifluoromethylphenyl
146	0	$NHSO_2CH_3$	CH_2	CH	CH	amino
147	0	$NHSO_2CH_3$	CH_2	CH	CH	amidino
148	0	$NHSO_2CH_3$	CH_2	CH	CH	guanidino
149	0	$NHSO_2CH_3$	CH_2	CH	CH	2-sulfamidophenyl
150	0	$NHSO_2CH_3$	CH_2	CH	CH	2-trifluoromethylphenyl
151	0	OCH_3	CH_2	CH	CH	amino
152	0	OCH_3	CH_2	CH	CH	amidino
153	0	OCH_3	CH_2	CH	CH	guanidino
154	0	OCH_3	CH_2	CH	CH	2-sulfamidophenyl
155	0	OCH_3	CH_2	CH	CH	2-trifluoromethylphenyl
156	0	$OCH_2C_6H_5$	CH_2	CH	CH	amino
157	0	$OCH_2C_6H_5$	CH_2	CH	CH	amidino
158	0	$OCH_2C_6H_5$	CH_2	CH	CH	guanidino
159	0	$OCH_2C_6H_5$	CH_2	CH	CH	2-sulfamidophenyl
160	0	$OCH_2C_6H_5$	CH_2	CH	CH	2-trifluoromethylphenyl
161	0	H	bond	N	CH	amino
162	0	H	bond	N	CH	amidino
163	0	H	bond	N	CH	guanidino
164	0	H	bond	N	CH	2-sulfamidophenyl
165	0	H	bond	N	CH	2-trifluoromethylphenyl
166	0	OH	bond	N	CH	amino
167	0	OH	bond	N	CH	amidino
168	0	OH	bond	N	CH	guanidino
169	0	OH	bond	N	CH	2-sulfamidophenyl
170	0	OH	bond	N	CH	2-trifluoromethylphenyl
171	0	NHC(O)CH_3	bond	N	CH	amino
172	0	NHC(O)CH_3	bond	N	CH	amidino
173	0	NHC(O)CH_3	bond	N	CH	guanidino
174	0	NHC(O)CH_3	bond	N	CH	2-sulfamidophenyl
175	0	NHC(O)CH_3	bond	N	CH	2-trifluoromethylphenyl
176	0	$NHSO_2CH_3$	bond	N	CH	amino
177	0	$NHSO_2CH_3$	bond	N	CH	amidino
178	0	$NHSO_2CH_3$	bond	N	CH	guanidino
179	0	$NHSO_2CH_3$	bond	N	CH	2-sulfamidophenyl
180	0	$NHSO_2CH_3$	bond	N	CH	2-trifluoromethylphenyl
181	0	OCH_3	bond	N	CH	amino
182	0	OCH_3	bond	N	CH	amidino
183	0	OCH_3	bond	N	CH	guanidino
184	0	OCH_3	bond	N	CH	2-sulfamidophenyl
185	0	OCH_3	bond	N	CH	2-trifluoromethylphenyl
186	0	$OCH_2C_6H_5$	bond	N	CH	amino
187	0	$OCH_2C_6H_5$	bond	N	CH	amidino
188	0	$OCH_2C_6H_5$	bond	N	CH	guanidino
189	0	$OCH_2C_6H_5$	bond	N	CH	2-sulfamidophenyl
190	0	$OCH_2C_6H_5$	bond	N	CH	2-trifluoromethylphenyl
191	0	H	CH_2	N	CH	amino
192	0	H	CH_2	N	CH	amidino
193	0	H	CH_2	N	CH	guanidino
194	0	H	CH_2	N	CH	2-sulfamidophenyl

195	0	H	CH_2	N	CH	2-trifluoromethylphenyl
196	0	OH	CH_2	N	CH	amino
197	0	OH	CH_2	N	CH	amidino
198	0	OH	CH_2	N	CH	guanidino
199	0	OH	CH_2	N	CH	2-sulfamidophenyl
200	0	OH	CH_2	N	CH	2-trifluoromethylphenyl
201	0	$NHC(O)CH_3$	CH_2	N	CH	amino
202	0	$NHC(O)CH_3$	CH_2	N	CH	amidino
203	0	$NHC(O)CH_3$	CH_2	N	CH	guanidino
204	0	$NHC(O)CH_3$	CH_2	N	CH	2-sulfamidophenyl
205	0	$NHC(O)CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
206	0	$NHSO_2CH_3$	CH_2	N	CH	amino
207	0	$NHSO_2CH_3$	CH_2	N	CH	amidino
208	0	$NHSO_2CH_3$	CH_2	N	CH	guanidino
209	0	$NHSO_2CH_3$	CH_2	N	CH	2-sulfamidophenyl
210	0	$NHSO_2CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
211	0	OCH_3	CH_2	N	CH	amino
212	0	OCH_3	CH_2	N	CH	amidino
213	0	OCH_3	CH_2	N	CH	guanidino
214	0	OCH_3	CH_2	N	CH	2-sulfamidophenyl
215	0	OCH_3	CH_2	N	CH	2-trifluoromethylphenyl
216	0	$OCH_2C_6H_5$	CH_2	N	CH	amino
217	0	$OCH_2C_6H_5$	CH_2	N	CH	amidino
218	0	$OCH_2C_6H_5$	CH_2	N	CH	guanidino
219	0	$OCH_2C_6H_5$	CH_2	N	CH	2-sulfamidophenyl
220	0	$OCH_2C_6H_5$	CH_2	N	CH	2-trifluoromethylphenyl
221	0	H	bond	N	N	amino
222	0	H	bond	N	N	amidino
223	0	H	bond	N	N	guanidino
224	0	H	bond	N	N	2-sulfamidophenyl
225	0	H	bond	N	N	2-trifluoromethylphenyl
226	0	OH	bond	N	N	amino
227	0	OH	bond	N	N	amidino
228	0	OH	bond	N	N	guanidino
229	0	OH	bond	N	N	2-sulfamidophenyl
230	0	OH	bond	N	N	2-trifluoromethylphenyl
231	0	$NHC(O)CH_3$	bond	N	N	amino
232	0	$NHC(O)CH_3$	bond	N	N	amidino
233	0	$NHC(O)CH_3$	bond	N	N	guanidino
234	0	$NHC(O)CH_3$	bond	N	N	2-sulfamidophenyl
235	0	$NHC(O)CH_3$	bond	N	N	2-trifluoromethylphenyl
236	0	$NHSO_2CH_3$	bond	N	N	amino
237	0	$NHSO_2CH_3$	bond	N	N	amidino
238	0	$NHSO_2CH_3$	bond	N	N	guanidino
239	0	$NHSO_2CH_3$	bond	N	N	2-sulfamidophenyl
240	0	$NHSO_2CH_3$	bond	N	N	2-trifluoromethylphenyl
241	0	OCH_3	bond	N	N	amino
242	0	OCH_3	bond	N	N	amidino
243	0	OCH_3	bond	N	N	guanidino
244	0	OCH_3	bond	N	N	2-sulfamidophenyl
245	0	OCH_3	bond	N	N	2-trifluoromethylphenyl
246	0	$OCH_2C_6H_5$	bond	N	N	amino
247	0	$OCH_2C_6H_5$	bond	N	N	amidino

248	0	$OCH_2C_6H_5$	bond	N	N	guanidino
249	0	$OCH_2C_6H_5$	bond	N	N	2-sulfamidophenyl
250	0	$OCH_2C_6H_5$	bond	N	N	2-trifluoromethylphenyl
251	0	H	CH_2	N	N	amino
252	0	H	CH_2	N	N	amidino
253	0	H	CH_2	N	N	guanidino
254	0	H	CH_2	N	N	2-sulfamidophenyl
255	0	H	CH_2	N	N	2-trifluoromethylphenyl
256	0	OH	CH_2	N	N	amino
257	0	OH	CH_2	N	N	amidino
258	0	OH	CH_2	N	N	guanidino
259	0	OH	CH_2	N	N	2-sulfamidophenyl
260	0	OH	CH_2	N	N	2-trifluoromethylphenyl
261	0	$NHC(O)CH_3$	CH_2	N	N	amino
262	0	$NHC(O)CH_3$	CH_2	N	N	amidino
263	0	$NHC(O)CH_3$	CH_2	N	N	guanidino
264	0	$NHC(O)CH_3$	CH_2	N	N	2-sulfamidophenyl
265	0	$NHC(O)CH_3$	CH_2	N	N	2-trifluoromethylphenyl
266	0	$NHSO_2CH_3$	CH_2	N	N	amino
267	0	$NHSO_2CH_3$	CH_2	N	N	amidino
268	0	$NHSO_2CH_3$	CH_2	N	N	guanidino
269	0	$NHSO_2CH_3$	CH_2	N	N	2-sulfamidophenyl
270	0	$NHSO_2CH_3$	CH_2	N	N	2-trifluoromethylphenyl
271	0	OCH_3	CH_2	N	N	amino
272	0	OCH_3	CH_2	N	N	amidino
273	0	OCH_3	CH_2	N	N	guanidino
274	0	OCH_3	CH_2	N	N	2-sulfamidophenyl
275	0	OCH_3	CH_2	N	N	2-trifluoromethylphenyl
276	0	$OCH_2C_6H_5$	CH_2	N	N	amino
277	0	$OCH_2C_6H_5$	CH_2	N	N	amidino
278	0	$OCH_2C_6H_5$	CH_2	N	N	guanidino
279	0	$OCH_2C_6H_5$	CH_2	N	N	2-sulfamidophenyl
280	0	$OCH_2C_6H_5$	CH_2	N	N	2-trifluoromethylphenyl

Table 9



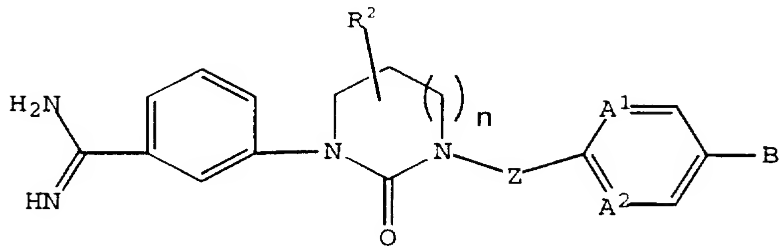
Ex.	n	R^2	Z	A^1	A^2	B
301	1	H	bond	CH	CH	amino
302	1	H	bond	CH	CH	amidino
303	1	H	bond	CH	CH	guanidino
304	1	H	bond	CH	CH	2-sulfamidophenyl
305	1	H	bond	CH	CH	2-trifluoromethylphenyl
306	1	OH	bond	CH	CH	amino
307	1	OH	bond	CH	CH	amidino
308	1	OH	bond	CH	CH	guanidino
309	1	OH	bond	CH	CH	2-sulfamidophenyl
310	1	OH	bond	CH	CH	2-trifluoromethylphenyl
311	1	$NHC(O)CH_3$	bond	CH	CH	amino
312	1	$NHC(O)CH_3$	bond	CH	CH	amidino
313	1	$NHC(O)CH_3$	bond	CH	CH	guanidino
314	1	$NHC(O)CH_3$	bond	CH	CH	2-sulfamidophenyl
315	1	$NHC(O)CH_3$	bond	CH	CH	2-trifluoromethylphenyl
316	1	$NHSO_2CH_3$	bond	CH	CH	amino
317	1	$NHSO_2CH_3$	bond	CH	CH	amidino
318	1	$NHSO_2CH_3$	bond	CH	CH	guanidino
319	1	$NHSO_2CH_3$	bond	CH	CH	2-sulfamidophenyl
320	1	$NHSO_2CH_3$	bond	CH	CH	2-trifluoromethylphenyl
321	1	OCH_3	bond	CH	CH	amino
322	1	OCH_3	bond	CH	CH	amidino
323	1	OCH_3	bond	CH	CH	guanidino
324	1	OCH_3	bond	CH	CH	2-sulfamidophenyl
325	1	OCH_3	bond	CH	CH	2-trifluoromethylphenyl
326	1	$OCH_2C_6H_5$	bond	CH	CH	amino
327	1	$OCH_2C_6H_5$	bond	CH	CH	amidino
328	1	$OCH_2C_6H_5$	bond	CH	CH	guanidino
329	1	$OCH_2C_6H_5$	bond	CH	CH	2-sulfamidophenyl
330	1	$OCH_2C_6H_5$	bond	CH	CH	2-trifluoromethylphenyl
331	1	H	CH_2	CH	CH	amino
332	1	H	CH_2	CH	CH	amidino
333	1	H	CH_2	CH	CH	guanidino
334	1	H	CH_2	CH	CH	2-sulfamidophenyl
335	1	H	CH_2	CH	CH	2-trifluoromethylphenyl
336	1	OH	CH_2	CH	CH	amino
337	1	OH	CH_2	CH	CH	amidino
338	1	OH	CH_2	CH	CH	guanidino
339	1	OH	CH_2	CH	CH	2-sulfamidophenyl
340	1	OH	CH_2	CH	CH	2-trifluoromethylphenyl
341	1	$NHC(O)CH_3$	CH_2	CH	CH	amino

342	1	$NHC(O)CH_3$	CH_2	CH	CH	amidino
343	1	$NHC(O)CH_3$	CH_2	CH	CH	guanidino
344	1	$NHC(O)CH_3$	CH_2	CH	CH	2-sulfamidophenyl
345	1	$NHC(O)CH_3$	CH_2	CH	CH	2-trifluoromethylphenyl
346	1	$NHSO_2CH_3$	CH_2	CH	CH	amino
347	1	$NHSO_2CH_3$	CH_2	CH	CH	amidino
348	1	$NHSO_2CH_3$	CH_2	CH	CH	guanidino
349	1	$NHSO_2CH_3$	CH_2	CH	CH	2-sulfamidophenyl
350	1	$NHSO_2CH_3$	CH_2	CH	CH	2-trifluoromethylphenyl
351	1	OCH_3	CH_2	CH	CH	amino
352	1	OCH_3	CH_2	CH	CH	amidino
353	1	OCH_3	CH_2	CH	CH	guanidino
354	1	OCH_3	CH_2	CH	CH	2-sulfamidophenyl
355	1	OCH_3	CH_2	CH	CH	2-trifluoromethylphenyl
356	1	$OCH_2C_6H_5$	CH_2	CH	CH	amino
357	1	$OCH_2C_6H_5$	CH_2	CH	CH	amidino
358	1	$OCH_2C_6H_5$	CH_2	CH	CH	guanidino
359	1	$OCH_2C_6H_5$	CH_2	CH	CH	2-sulfamidophenyl
360	1	$OCH_2C_6H_5$	CH_2	CH	CH	2-trifluoromethylphenyl
361	1	H	bond	N	CH	amino
362	1	H	bond	N	CH	amidino
363	1	H	bond	N	CH	guanidino
364	1	H	bond	N	CH	2-sulfamidophenyl
365	1	H	bond	N	CH	2-trifluoromethylphenyl
366	1	OH	bond	N	CH	amino
367	1	OH	bond	N	CH	amidino
368	1	OH	bond	N	CH	guanidino
369	1	OH	bond	N	CH	2-sulfamidophenyl
370	1	OH	bond	N	CH	2-trifluoromethylphenyl
371	1	$NHC(O)CH_3$	bond	N	CH	amino
372	1	$NHC(O)CH_3$	bond	N	CH	amidino
373	1	$NHC(O)CH_3$	bond	N	CH	guanidino
374	1	$NHC(O)CH_3$	bond	N	CH	2-sulfamidophenyl
375	1	$NHC(O)CH_3$	bond	N	CH	2-trifluoromethylphenyl
376	1	$NHSO_2CH_3$	bond	N	CH	amino
377	1	$NHSO_2CH_3$	bond	N	CH	amidino
378	1	$NHSO_2CH_3$	bond	N	CH	guanidino
379	1	$NHSO_2CH_3$	bond	N	CH	2-sulfamidophenyl
380	1	$NHSO_2CH_3$	bond	N	CH	2-trifluoromethylphenyl
381	1	OCH_3	bond	N	CH	amino
382	1	OCH_3	bond	N	CH	amidino
383	1	OCH_3	bond	N	CH	guanidino
384	1	OCH_3	bond	N	CH	2-sulfamidophenyl
385	1	OCH_3	bond	N	CH	2-trifluoromethylphenyl
386	1	$OCH_2C_6H_5$	bond	N	CH	amino
387	1	$OCH_2C_6H_5$	bond	N	CH	amidino
388	1	$OCH_2C_6H_5$	bond	N	CH	guanidino
389	1	$OCH_2C_6H_5$	bond	N	CH	2-sulfamidophenyl
390	1	$OCH_2C_6H_5$	bond	N	CH	2-trifluoromethylphenyl
391	1	H	CH_2	N	CH	amino
392	1	H	CH_2	N	CH	amidino
393	1	H	CH_2	N	CH	guanidino
394	1	H	CH_2	N	CH	2-sulfamidophenyl

395	1	H	CH_2	N	CH	2-trifluoromethylphenyl
396	1	OH	CH_2	N	CH	amino
397	1	OH	CH_2	N	CH	amidino
398	1	OH	CH_2	N	CH	guanidino
399	1	OH	CH_2	N	CH	2-sulfamidophenyl
400	1	OH	CH_2	N	CH	2-trifluoromethylphenyl
401	1	$NHC(O)CH_3$	CH_2	N	CH	amino
402	1	$NHC(O)CH_3$	CH_2	N	CH	amidino
403	1	$NHC(O)CH_3$	CH_2	N	CH	guanidino
404	1	$NHC(O)CH_3$	CH_2	N	CH	2-sulfamidophenyl
405	1	$NHC(O)CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
406	1	$NHSO_2CH_3$	CH_2	N	CH	amino
407	1	$NHSO_2CH_3$	CH_2	N	CH	amidino
408	1	$NHSO_2CH_3$	CH_2	N	CH	guanidino
409	1	$NHSO_2CH_3$	CH_2	N	CH	2-sulfamidophenyl
410	1	$NHSO_2CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
411	1	OCH_3	CH_2	N	CH	amino
412	1	OCH_3	CH_2	N	CH	amidino
413	1	OCH_3	CH_2	N	CH	guanidino
414	1	OCH_3	CH_2	N	CH	2-sulfamidophenyl
415	1	OCH_3	CH_2	N	CH	2-trifluoromethylphenyl
416	1	$OCH_2C_6H_5$	CH_2	N	CH	amino
417	1	$OCH_2C_6H_5$	CH_2	N	CH	amidino
418	1	$OCH_2C_6H_5$	CH_2	N	CH	guanidino
419	1	$OCH_2C_6H_5$	CH_2	N	CH	2-sulfamidophenyl
420	1	$OCH_2C_6H_5$	CH_2	N	CH	2-trifluoromethylphenyl
421	1	H	bond	N	N	amino
422	1	H	bond	N	N	amidino
423	1	H	bond	N	N	guanidino
424	1	H	bond	N	N	2-sulfamidophenyl
425	1	H	bond	N	N	2-trifluoromethylphenyl
426	1	OH	bond	N	N	amino
427	1	OH	bond	N	N	amidino
428	1	OH	bond	N	N	guanidino
429	1	OH	bond	N	N	2-sulfamidophenyl
430	1	OH	bond	N	N	2-trifluoromethylphenyl
431	1	$NHC(O)CH_3$	bond	N	N	amino
432	1	$NHC(O)CH_3$	bond	N	N	amidino
433	1	$NHC(O)CH_3$	bond	N	N	guanidino
434	1	$NHC(O)CH_3$	bond	N	N	2-sulfamidophenyl
435	1	$NHC(O)CH_3$	bond	N	N	2-trifluoromethylphenyl
436	1	$NHSO_2CH_3$	bond	N	N	amino
437	1	$NHSO_2CH_3$	bond	N	N	amidino
438	1	$NHSO_2CH_3$	bond	N	N	guanidino
439	1	$NHSO_2CH_3$	bond	N	N	2-sulfamidophenyl
440	1	$NHSO_2CH_3$	bond	N	N	2-trifluoromethylphenyl
441	1	OCH_3	bond	N	N	amino
442	1	OCH_3	bond	N	N	amidino
443	1	OCH_3	bond	N	N	guanidino
444	1	OCH_3	bond	N	N	2-sulfamidophenyl
445	1	OCH_3	bond	N	N	2-trifluoromethylphenyl
446	1	$OCH_2C_6H_5$	bond	N	N	amino
447	1	$OCH_2C_6H_5$	bond	N	N	amidino

448	1	$OCH_2C_6H_5$	bond	N	N	guanidino
449	1	$OCH_2C_6H_5$	bond	N	N	2-sulfamidophenyl
450	1	$OCH_2C_6H_5$	bond	N	N	2-trifluoromethylphenyl
451	1	H	CH_2	N	N	amino
452	1	H	CH_2	N	N	amidino
453	1	H	CH_2	N	N	guanidino
454	1	H	CH_2	N	N	2-sulfamidophenyl
455	1	H	CH_2	N	N	2-trifluoromethylphenyl
456	1	OH	CH_2	N	N	amino
457	1	OH	CH_2	N	N	amidino
458	1	OH	CH_2	N	N	guanidino
459	1	OH	CH_2	N	N	2-sulfamidophenyl
460	1	OH	CH_2	N	N	2-trifluoromethylphenyl
461	1	$NHC(O)CH_3$	CH_2	N	N	amino
462	1	$NHC(O)CH_3$	CH_2	N	N	amidino
463	1	$NHC(O)CH_3$	CH_2	N	N	guanidino
464	1	$NHC(O)CH_3$	CH_2	N	N	2-sulfamidophenyl
465	1	$NHC(O)CH_3$	CH_2	N	N	2-trifluoromethylphenyl
466	1	$NHSO_2CH_3$	CH_2	N	N	amino
467	1	$NHSO_2CH_3$	CH_2	N	N	amidino
468	1	$NHSO_2CH_3$	CH_2	N	N	guanidino
469	1	$NHSO_2CH_3$	CH_2	N	N	2-sulfamidophenyl
470	1	$NHSO_2CH_3$	CH_2	N	N	2-trifluoromethylphenyl
471	1	OCH_3	CH_2	N	N	amino
472	1	OCH_3	CH_2	N	N	amidino
473	1	OCH_3	CH_2	N	N	guanidino
474	1	OCH_3	CH_2	N	N	2-sulfamidophenyl
475	1	OCH_3	CH_2	N	N	2-trifluoromethylphenyl
476	1	$OCH_2C_6H_5$	CH_2	N	N	amino
477	1	$OCH_2C_6H_5$	CH_2	N	N	amidino
478	1	$OCH_2C_6H_5$	CH_2	N	N	guanidino
479	1	$OCH_2C_6H_5$	CH_2	N	N	2-sulfamidophenyl
480	1	$OCH_2C_6H_5$	CH_2	N	N	2-trifluoromethylphenyl

Table 10



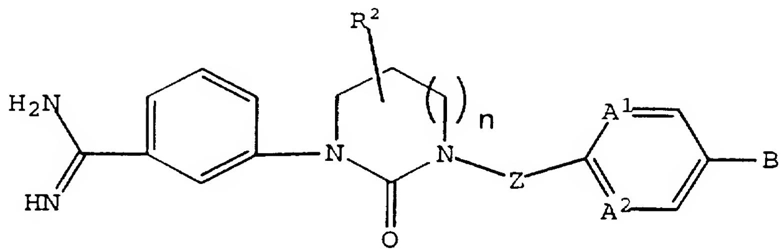
Ex.	n	R^2	Z	A^1	A^2	B
501	2	H	bond	CH	CH	amino
502	2	H	bond	CH	CH	guanidino
503	2	H	bond	CH	CH	2-sulfamidophenyl
504	2	H	bond	CH	CH	2-trifluoromethylphenyl
505	2	OH	bond	CH	CH	amino
506	2	OH	bond	CH	CH	amidino
507	2	OH	bond	CH	CH	guanidino
508	2	OH	bond	CH	CH	2-sulfamidophenyl
509	2	OH	bond	CH	CH	2-trifluoromethylphenyl
510	2	$NHC(O)CH_3$	bond	CH	CH	amino
511	2	$NHC(O)CH_3$	bond	CH	CH	amidino
512	2	$NHC(O)CH_3$	bond	CH	CH	guanidino
513	2	$NHC(O)CH_3$	bond	CH	CH	2-sulfamidophenyl
514	2	$NHC(O)CH_3$	bond	CH	CH	2-trifluoromethylphenyl
515	2	$NHSO_2CH_3$	bond	CH	CH	amino
516	2	$NHSO_2CH_3$	bond	CH	CH	amidino
517	2	$NHSO_2CH_3$	bond	CH	CH	guanidino
518	2	$NHSO_2CH_3$	bond	CH	CH	2-sulfamidophenyl
519	2	$NHSO_2CH_3$	bond	CH	CH	2-trifluoromethylphenyl
520	2	OCH_3	bond	CH	CH	amino
521	2	OCH_3	bond	CH	CH	amidino
522	2	OCH_3	bond	CH	CH	guanidino
523	2	OCH_3	bond	CH	CH	2-sulfamidophenyl
524	2	OCH_3	bond	CH	CH	2-trifluoromethylphenyl
525	2	$OCH_2C_6H_5$	bond	CH	CH	amino
526	2	$OCH_2C_6H_5$	bond	CH	CH	amidino
527	2	$OCH_2C_6H_5$	bond	CH	CH	guanidino
528	2	$OCH_2C_6H_5$	bond	CH	CH	2-sulfamidophenyl
529	2	$OCH_2C_6H_5$	bond	CH	CH	2-trifluoromethylphenyl
530	2	H	CH_2	CH	CH	amino
531	2	H	CH_2	CH	CH	guanidino
532	2	H	CH_2	CH	CH	2-sulfamidophenyl
533	2	H	CH_2	CH	CH	2-trifluoromethylphenyl
534	2	OH	CH_2	CH	CH	amino
535	2	OH	CH_2	CH	CH	amidino
536	2	OH	CH_2	CH	CH	guanidino
537	2	OH	CH_2	CH	CH	2-sulfamidophenyl
538	2	OH	CH_2	CH	CH	2-trifluoromethylphenyl
539	2	$NHC(O)CH_3$	CH_2	CH	CH	amino
540	2	$NHC(O)CH_3$	CH_2	CH	CH	amidino
541	2	$NHC(O)CH_3$	CH_2	CH	CH	guanidino

542	2	NHC(O)CH_3	CH_2	CH	CH	2-sulfamidophenyl
543	2	NHC(O)CH_3	CH_2	CH	CH	2-trifluoromethylphenyl
544	2	$NHSO_2CH_3$	CH_2	CH	CH	amino
545	2	$NHSO_2CH_3$	CH_2	CH	CH	amidino
546	2	$NHSO_2CH_3$	CH_2	CH	CH	guanidino
547	2	$NHSO_2CH_3$	CH_2	CH	CH	2-sulfamidophenyl
548	2	$NHSO_2CH_3$	CH_2	CH	CH	2-trifluoromethylphenyl
549	2	OCH_3	CH_2	CH	CH	amino
550	2	OCH_3	CH_2	CH	CH	amidino
551	2	OCH_3	CH_2	CH	CH	guanidino
552	2	OCH_3	CH_2	CH	CH	2-sulfamidophenyl
553	2	OCH_3	CH_2	CH	CH	2-trifluoromethylphenyl
554	2	$OCH_2C_6H_5$	CH_2	CH	CH	amino
555	2	$OCH_2C_6H_5$	CH_2	CH	CH	amidino
556	2	$OCH_2C_6H_5$	CH_2	CH	CH	guanidino
557	2	$OCH_2C_6H_5$	CH_2	CH	CH	2-sulfamidophenyl
558	2	$OCH_2C_6H_5$	CH_2	CH	CH	2-trifluoromethylphenyl
559	2	H	bond	N	CH	amino
560	2	H	bond	N	CH	amidino
561	2	H	bond	N	CH	guanidino
562	2	H	bond	N	CH	2-sulfamidophenyl
563	2	H	bond	N	CH	2-trifluoromethylphenyl
564	2	OH	bond	N	CH	amino
565	2	OH	bond	N	CH	amidino
566	2	OH	bond	N	CH	guanidino
567	2	OH	bond	N	CH	2-sulfamidophenyl
568	2	OH	bond	N	CH	2-trifluoromethylphenyl
569	2	NHC(O)CH_3	bond	N	CH	amino
570	2	NHC(O)CH_3	bond	N	CH	amidino
571	2	NHC(O)CH_3	bond	N	CH	guanidino
572	2	NHC(O)CH_3	bond	N	CH	2-sulfamidophenyl
573	2	NHC(O)CH_3	bond	N	CH	2-trifluoromethylphenyl
574	2	$NHSO_2CH_3$	bond	N	CH	amino
575	2	$NHSO_2CH_3$	bond	N	CH	amidino
576	2	$NHSO_2CH_3$	bond	N	CH	guanidino
577	2	$NHSO_2CH_3$	bond	N	CH	2-sulfamidophenyl
578	2	$NHSO_2CH_3$	bond	N	CH	2-trifluoromethylphenyl
579	2	OCH_3	bond	N	CH	amino
580	2	OCH_3	bond	N	CH	amidino
581	2	OCH_3	bond	N	CH	guanidino
582	2	OCH_3	bond	N	CH	2-sulfamidophenyl
583	2	OCH_3	bond	N	CH	2-trifluoromethylphenyl
584	2	$OCH_2C_6H_5$	bond	N	CH	amino
585	2	$OCH_2C_6H_5$	bond	N	CH	amidino
586	2	$OCH_2C_6H_5$	bond	N	CH	guanidino
587	2	$OCH_2C_6H_5$	bond	N	CH	2-sulfamidophenyl
588	2	$OCH_2C_6H_5$	bond	N	CH	2-trifluoromethylphenyl
589	2	H	CH_2	N	CH	amino
590	2	H	CH_2	N	CH	amidino
591	2	H	CH_2	N	CH	guanidino
592	2	H	CH_2	N	CH	2-sulfamidophenyl
593	2	H	CH_2	N	CH	2-trifluoromethylphenyl
594	2	OH	CH_2	N	CH	amino

595	2	OH	CH_2	N	CH	amidino
596	2	OH	CH_2	N	CH	guanidino
597	2	OH	CH_2	N	CH	2-sulfamidophenyl
598	2	OH	CH_2	N	CH	2-trifluoromethylphenyl
599	2	$NHC(O)CH_3$	CH_2	N	CH	amino
600	2	$NHC(O)CH_3$	CH_2	N	CH	amidino
601	2	$NHC(O)CH_3$	CH_2	N	CH	guanidino
602	2	$NHC(O)CH_3$	CH_2	N	CH	2-sulfamidophenyl
603	2	$NHC(O)CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
604	2	$NHSO_2CH_3$	CH_2	N	CH	amino
605	2	$NHSO_2CH_3$	CH_2	N	CH	amidino
606	2	$NHSO_2CH_3$	CH_2	N	CH	guanidino
607	2	$NHSO_2CH_3$	CH_2	N	CH	2-sulfamidophenyl
608	2	$NHSO_2CH_3$	CH_2	N	CH	2-trifluoromethylphenyl
609	2	OCH_3	CH_2	N	CH	amino
610	2	OCH_3	CH_2	N	CH	amidino
611	2	OCH_3	CH_2	N	CH	guanidino
612	2	OCH_3	CH_2	N	CH	2-sulfamidophenyl
613	2	OCH_3	CH_2	N	CH	2-trifluoromethylphenyl
614	2	$OCH_2C_6H_5$	CH_2	N	CH	amino
615	2	$OCH_2C_6H_5$	CH_2	N	CH	amidino
616	2	$OCH_2C_6H_5$	CH_2	N	CH	guanidino
617	2	$OCH_2C_6H_5$	CH_2	N	CH	2-sulfamidophenyl
618	2	$OCH_2C_6H_5$	CH_2	N	CH	2-trifluoromethylphenyl
619	2	H	bond	N	N	amino
620	2	H	bond	N	N	amidino
621	2	H	bond	N	N	guanidino
622	2	H	bond	N	N	2-sulfamidophenyl
623	2	H	bond	N	N	2-trifluoromethylphenyl
624	2	OH	bond	N	N	amino
625	2	OH	bond	N	N	amidino
626	2	OH	bond	N	N	guanidino
627	2	OH	bond	N	N	2-sulfamidophenyl
628	2	OH	bond	N	N	2-trifluoromethylphenyl
629	2	$NHC(O)CH_3$	bond	N	N	amino
630	2	$NHC(O)CH_3$	bond	N	N	amidino
631	2	$NHC(O)CH_3$	bond	N	N	guanidino
632	2	$NHC(O)CH_3$	bond	N	N	2-sulfamidophenyl
633	2	$NHC(O)CH_3$	bond	N	N	2-trifluoromethylphenyl
634	2	$NHSO_2CH_3$	bond	N	N	amino
635	2	$NHSO_2CH_3$	bond	N	N	amidino
636	2	$NHSO_2CH_3$	bond	N	N	guanidino
637	2	$NHSO_2CH_3$	bond	N	N	2-sulfamidophenyl
638	2	$NHSO_2CH_3$	bond	N	N	2-trifluoromethylphenyl
639	2	OCH_3	bond	N	N	amino
640	2	OCH_3	bond	N	N	amidino
641	2	OCH_3	bond	N	N	guanidino
642	2	OCH_3	bond	N	N	2-sulfamidophenyl
643	2	OCH_3	bond	N	N	2-trifluoromethylphenyl
644	2	$OCH_2C_6H_5$	bond	N	N	amino
645	2	$OCH_2C_6H_5$	bond	N	N	amidino
646	2	$OCH_2C_6H_5$	bond	N	N	guanidino
647	2	$OCH_2C_6H_5$	bond	N	N	2-sulfamidophenyl

648	2	$OCH_2C_6H_5$	bond	N	N	2-trifluoromethylphenyl
649	2	H	CH_2	N	N	amino
650	2	H	CH_2	N	N	amidino
651	2	H	CH_2	N	N	guanidino
652	2	H	CH_2	N	N	2-sulfamidophenyl
653	2	H	CH_2	N	N	2-trifluoromethylphenyl
654	2	OH	CH_2	N	N	amino
655	2	OH	CH_2	N	N	amidino
656	2	OH	CH_2	N	N	guanidino
657	2	OH	CH_2	N	N	2-sulfamidophenyl
658	2	OH	CH_2	N	N	2-trifluoromethylphenyl
659	2	$NHC(O)CH_3$	CH_2	N	N	amino
660	2	$NHC(O)CH_3$	CH_2	N	N	amidino
661	2	$NHC(O)CH_3$	CH_2	N	N	guanidino
662	2	$NHC(O)CH_3$	CH_2	N	N	2-sulfamidophenyl
663	2	$NHC(O)CH_3$	CH_2	N	N	2-trifluoromethylphenyl
664	2	$NHSO_2CH_3$	CH_2	N	N	amino
665	2	$NHSO_2CH_3$	CH_2	N	N	amidino
666	2	$NHSO_2CH_3$	CH_2	N	N	guanidino
667	2	$NHSO_2CH_3$	CH_2	N	N	2-sulfamidophenyl
668	2	$NHSO_2CH_3$	CH_2	N	N	2-trifluoromethylphenyl
669	2	OCH_3	CH_2	N	N	amino
670	2	OCH_3	CH_2	N	N	amidino
671	2	OCH_3	CH_2	N	N	guanidino
672	2	OCH_3	CH_2	N	N	2-sulfamidophenyl
673	2	OCH_3	CH_2	N	N	2-trifluoromethylphenyl
674	2	$OCH_2C_6H_5$	CH_2	N	N	amino
675	2	$OCH_2C_6H_5$	CH_2	N	N	amidino
676	2	$OCH_2C_6H_5$	CH_2	N	N	guanidino
677	2	$OCH_2C_6H_5$	CH_2	N	N	2-sulfamidophenyl
678	2	$OCH_2C_6H_5$	CH_2	N	N	2-trifluoromethylphenyl

Table 11



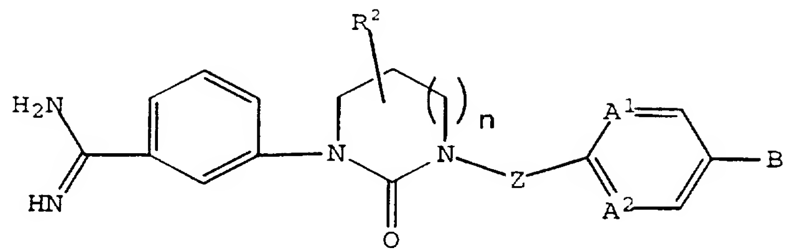
Ex.	n	R^2	Z	A^1	A^2	B
701	0	H	bond	CH	CH	imidazol-1-yl
702	0	H	bond	CH	CH	morpholin-1-yl
703	0	H	bond	CH	CH	2-methylimidazol-1-yl
704	0	H	bond	CH	CH	pyridin-3-yl
705	0	H	bond	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
706	0	H	bond	CH	CH	pyrazol-1-yl
707	0	H	bond	CH	CH	phenyl
708	0	H	bond	CH	CH	cyclohexyl
709	0	H	bond	CH	CH	N,N-dimethylsulfamido
710	0	H	bond	CH	CH	N,N-dimethylamido
711	0	H	bond	N	CH	imidazol-1-yl
712	0	H	bond	N	CH	morpholin-1-yl
713	0	H	bond	N	CH	2-methylimidazol-1-yl
714	0	H	bond	N	CH	pyridin-3-yl
715	0	H	bond	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
716	0	H	bond	N	CH	pyrazol-1-yl
717	0	H	bond	N	CH	phenyl
718	0	H	bond	N	CH	cyclohexyl
719	0	H	bond	N	CH	N,N-dimethylsulfamido
720	0	H	bond	N	CH	N,N-dimethylamido
721	0	H	bond	N	N	imidazol-1-yl
722	0	H	bond	N	N	morpholin-1-yl
723	0	H	bond	N	N	2-methylimidazol-1-yl
724	0	H	bond	N	N	pyridin-3-yl
725	0	H	bond	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
726	0	H	bond	N	N	pyrazol-1-yl
727	0	H	bond	N	N	phenyl
728	0	H	bond	N	N	cyclohexyl
729	0	H	bond	N	N	N,N-dimethylsulfamido
730	0	H	bond	N	N	N,N-dimethylamido
731	0	H	bond	F	CH	imidazol-1-yl
732	0	H	bond	F	CH	morpholin-1-yl
733	0	H	bond	F	CH	2-methylimidazol-1-yl
734	0	H	bond	F	CH	pyridin-3-yl
735	0	H	bond	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
736	0	H	bond	F	CH	pyrazol-1-yl
737	0	H	bond	F	CH	phenyl
738	0	H	bond	F	CH	cyclohexyl
739	0	H	bond	F	CH	N,N-dimethylsulfamido
740	0	H	bond	F	CH	N,N-dimethylamido

741	0	H	bond	Cl	CH	imidazol-1-yl
742	0	H	bond	Cl	CH	morpholin-1-yl
743	0	H	bond	Cl	CH	2-methylimidazol-1-yl
744	0	H	bond	Cl	CH	pyridin-3-yl
745	0	H	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
746	0	H	bond	Cl	CH	pyrazol-1-yl
747	0	H	bond	Cl	CH	phenyl
748	0	H	bond	Cl	CH	cyclohexyl
749	0	H	bond	Cl	CH	N,N-dimethylsulfamido
750	0	H	bond	Cl	CH	N,N-dimethylamido
751	0	H	bond	Br	CH	imidazol-1-yl
752	0	H	bond	Br	CH	morpholin-1-yl
753	0	H	bond	Br	CH	2-methylimidazol-1-yl
754	0	H	bond	Br	CH	pyridin-3-yl
755	0	H	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
756	0	H	bond	Br	CH	pyrazol-1-yl
757	0	H	bond	Br	CH	phenyl
758	0	H	bond	Br	CH	cyclohexyl
759	0	H	bond	Br	CH	N,N-dimethylsulfamido
760	0	H	bond	Br	CH	N,N-dimethylamido
761	0	H	CH_2	CH	CH	imidazol-1-yl
762	0	H	CH_2	CH	CH	morpholin-1-yl
763	0	H	CH_2	CH	CH	2-methylimidazol-1-yl
764	0	H	CH_2	CH	CH	pyridin-3-yl
765	0	H	CH_2	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
766	0	H	CH_2	CH	CH	pyrazol-1-yl
767	0	H	CH_2	CH	CH	phenyl
768	0	H	CH_2	CH	CH	cyclohexyl
769	0	H	CH_2	CH	CH	N,N-dimethylsulfamido
770	0	H	CH_2	CH	CH	N,N-dimethylamido
771	0	H	CH_2	N	CH	imidazol-1-yl
772	0	H	CH_2	N	CH	morpholin-1-yl
773	0	H	CH_2	N	CH	2-methylimidazol-1-yl
774	0	H	CH_2	N	CH	pyridin-3-yl
775	0	H	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
776	0	H	CH_2	N	CH	pyrazol-1-yl
777	0	H	CH_2	N	CH	phenyl
778	0	H	CH_2	N	CH	cyclohexyl
779	0	H	CH_2	N	CH	N,N-dimethylsulfamido
780	0	H	CH_2	N	CH	N,N-dimethylamido
781	0	H	CH_2	N	N	imidazol-1-yl
782	0	H	CH_2	N	N	morpholin-1-yl
783	0	H	CH_2	N	N	2-methylimidazol-1-yl
784	0	H	CH_2	N	N	pyridin-3-yl
785	0	H	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
786	0	H	CH_2	N	N	pyrazol-1-yl
787	0	H	CH_2	N	N	phenyl
788	0	H	CH_2	N	N	cyclohexyl
789	0	H	CH_2	N	N	N,N-dimethylsulfamido

790	0	H	CH_2	N	N	N,N-dimethylamido
791	0	H	CH_2	F	CH	imidazol-1-yl
792	0	H	CH_2	F	CH	morpholin-1-yl
793	0	H	CH_2	F	CH	2-methylimidazol-1-yl
794	0	H	CH_2	F	CH	pyridin-3-yl
795	0	H	CH_2	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
796	0	H	CH_2	F	CH	pyrazol-1-yl
797	0	H	CH_2	F	CH	phenyl
798	0	H	CH_2	F	CH	cyclohexyl
799	0	H	CH_2	F	CH	N,N-dimethylsulfamido
800	0	H	CH_2	F	CH	N,N-dimethylamido
801	0	H	CH_2	Cl	CH	imidazol-1-yl
802	0	H	CH_2	Cl	CH	morpholin-1-yl
803	0	H	CH_2	Cl	CH	2-methylimidazol-1-yl
804	0	H	CH_2	Cl	CH	pyridin-3-yl
805	0	H	CH_2	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
806	0	H	CH_2	Cl	CH	pyrazol-1-yl
807	0	H	CH_2	Cl	CH	phenyl
808	0	H	CH_2	Cl	CH	cyclohexyl
809	0	H	CH_2	Cl	CH	N,N-dimethylsulfamido
810	0	H	CH_2	Cl	CH	N,N-dimethylamido
811	0	H	CH_2	Br	CH	imidazol-1-yl
812	0	H	CH_2	Br	CH	morpholin-1-yl
813	0	H	CH_2	Br	CH	2-methylimidazol-1-yl
814	0	H	CH_2	Br	CH	pyridin-3-yl
815	0	H	CH_2	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
816	0	H	CH_2	Br	CH	pyrazol-1-yl
817	0	H	CH_2	Br	CH	phenyl
818	0	H	CH_2	Br	CH	cyclohexyl
819	0	H	CH_2	Br	CH	N,N-dimethylsulfamido
820	0	H	CH_2	Br	CH	N,N-dimethylamido
821	0	OH	bond	F	CH	pyrazol-1-yl
822	0	OH	bond	F	CH	phenyl
823	0	OH	bond	F	CH	cyclohexyl
824	0	OH	bond	F	CH	N,N-dimethylsulfamido
825	0	OH	bond	F	CH	N,N-dimethylamido
826	0	$NHC(O)CH_3$	bond	Cl	CH	imidazol-1-yl
827	0	$NHC(O)CH_3$	bond	Cl	CH	morpholin-1-yl
828	0	$NHC(O)CH_3$	bond	Cl	CH	2-methylimidazol-1-yl
829	0	$NHC(O)CH_3$	bond	Cl	CH	pyridin-3-yl
830	0	$NHC(O)CH_3$	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
831	0	$NHSO_2CH_3$	bond	Cl	CH	pyrazol-1-yl
832	0	$NHSO_2CH_3$	bond	Cl	CH	phenyl
833	0	$NHSO_2CH_3$	bond	Cl	CH	cyclohexyl
834	0	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylsulfamido
835	0	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylamido
836	0	OCH_3	bond	Br	CH	imidazol-1-yl
837	0	OCH_3	bond	Br	CH	morpholin-1-yl
838	0	OCH_3	bond	Br	CH	2-methylimidazol-1-yl

839	0	OCH_3	bond	Br	CH	pyridin-3-yl
840	0	OCH_3	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
841	0	$OCH_2C_6H_5$	bond	Br	CH	pyrazol-1-yl
842	0	$OCH_2C_6H_5$	bond	Br	CH	phenyl
843	0	$OCH_2C_6H_5$	bond	Br	CH	cyclohexyl
844	0	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylsulfamido
845	0	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylamido
846	0	OH	CH_2	CH	CH	pyrazol-1-yl
847	0	OH	CH_2	CH	CH	phenyl
848	0	OH	CH_2	CH	CH	cyclohexyl
849	0	OH	CH_2	CH	CH	N,N-dimethylsulfamido
850	0	OH	CH_2	CH	CH	N,N-dimethylamido
851	0	$NHC(O)CH_3$	CH_2	N	CH	imidazol-1-yl
852	0	$NHC(O)CH_3$	CH_2	N	CH	morpholin-1-yl
853	0	$NHC(O)CH_3$	CH_2	N	CH	2-methylimidazol-1-yl
854	0	$NHC(O)CH_3$	CH_2	N	CH	pyridin-3-yl
855	0	$NHC(O)CH_3$	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
856	0	$NHSO_2CH_3$	CH_2	N	CH	pyrazol-1-yl
857	0	$NHSO_2CH_3$	CH_2	N	CH	phenyl
858	0	$NHSO_2CH_3$	CH_2	N	CH	cyclohexyl
859	0	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylsulfamido
860	0	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylamido
861	0	OCH_3	CH_2	N	N	imidazol-1-yl
862	0	OCH_3	CH_2	N	N	morpholin-1-yl
863	0	OCH_3	CH_2	N	N	2-methylimidazol-1-yl
864	0	OCH_3	CH_2	N	N	pyridin-3-yl
865	0	OCH_3	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
866	0	$OCH_2C_6H_5$	CH_2	N	N	pyrazol-1-yl
867	0	$OCH_2C_6H_5$	CH_2	N	N	phenyl
868	0	$OCH_2C_6H_5$	CH_2	N	N	cyclohexyl
869	0	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylsulfamido
870	0	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylamido

Table 12



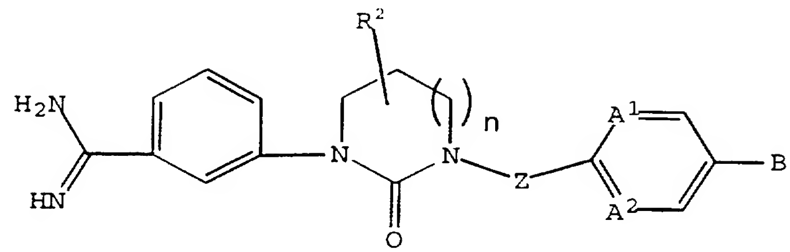
Ex.	n	R^2	Z	A^1	A^2	B
901	1	H	bond	CH	CH	imidazol-1-yl
902	1	H	bond	CH	CH	morpholin-1-yl
903	1	H	bond	CH	CH	2-methylimidazol-1-yl
904	1	H	bond	CH	CH	pyridin-3-yl
905	1	H	bond	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
906	1	H	bond	CH	CH	pyrazol-1-yl
907	1	H	bond	CH	CH	phenyl
908	1	H	bond	CH	CH	cyclohexyl
909	1	H	bond	CH	CH	N,N-dimethylsulfamido
910	1	H	bond	CH	CH	N,N-dimethylamido
911	1	H	bond	N	CH	imidazol-1-yl
912	1	H	bond	N	CH	morpholin-1-yl
913	1	H	bond	N	CH	2-methylimidazol-1-yl
914	1	H	bond	N	CH	pyridin-3-yl
915	1	H	bond	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
916	1	H	bond	N	CH	pyrazol-1-yl
917	1	H	bond	N	CH	phenyl
918	1	H	bond	N	CH	cyclohexyl
919	1	H	bond	N	CH	N,N-dimethylsulfamido
920	1	H	bond	N	CH	N,N-dimethylamido
921	1	H	bond	N	N	imidazol-1-yl
922	1	H	bond	N	N	morpholin-1-yl
923	1	H	bond	N	N	2-methylimidazol-1-yl
924	1	H	bond	N	N	pyridin-3-yl
925	1	H	bond	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
926	1	H	bond	N	N	pyrazol-1-yl
927	1	H	bond	N	N	phenyl
928	1	H	bond	N	N	cyclohexyl
929	1	H	bond	N	N	N,N-dimethylsulfamido
930	1	H	bond	N	N	N,N-dimethylamido
931	1	H	bond	F	CH	imidazol-1-yl
932	1	H	bond	F	CH	morpholin-1-yl
933	1	H	bond	F	CH	2-methylimidazol-1-yl
934	1	H	bond	F	CH	pyridin-3-yl
935	1	H	bond	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
936	1	H	bond	F	CH	pyrazol-1-yl
937	1	H	bond	F	CH	phenyl
938	1	H	bond	F	CH	cyclohexyl
939	1	H	bond	F	CH	N,N-dimethylsulfamido
940	1	H	bond	F	CH	N,N-dimethylamido

941	1	H	bond	Cl	CH	imidazol-1-yl
942	1	H	bond	Cl	CH	morpholin-1-yl
943	1	H	bond	Cl	CH	2-methylimidazol-1-yl
944	1	H	bond	Cl	CH	pyridin-3-yl
945	1	H	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
946	1	H	bond	Cl	CH	pyrazol-1-yl
947	1	H	bond	Cl	CH	phenyl
948	1	H	bond	Cl	CH	cyclohexyl
949	1	H	bond	Cl	CH	N,N-dimethylsulfamido
950	1	H	bond	Cl	CH	N,N-dimethylamido
951	1	H	bond	Br	CH	imidazol-1-yl
952	1	H	bond	Br	CH	morpholin-1-yl
953	1	H	bond	Br	CH	2-methylimidazol-1-yl
954	1	H	bond	Br	CH	pyridin-3-yl
955	1	H	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
956	1	H	bond	Br	CH	pyrazol-1-yl
957	1	H	bond	Br	CH	phenyl
958	1	H	bond	Br	CH	cyclohexyl
959	1	H	bond	Br	CH	N,N-dimethylsulfamido
960	1	H	bond	Br	CH	N,N-dimethylamido
961	1	H	CH_2	CH	CH	imidazol-1-yl
962	1	H	CH_2	CH	CH	morpholin-1-yl
963	1	H	CH_2	CH	CH	2-methylimidazol-1-yl
964	1	H	CH_2	CH	CH	pyridin-3-yl
965	1	H	CH_2	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
966	1	H	CH_2	CH	CH	pyrazol-1-yl
967	1	H	CH_2	CH	CH	phenyl
968	1	H	CH_2	CH	CH	cyclohexyl
969	1	H	CH_2	CH	CH	N,N-dimethylsulfamido
970	1	H	CH_2	CH	CH	N,N-dimethylamido
971	1	H	CH_2	N	CH	imidazol-1-yl
972	1	H	CH_2	N	CH	morpholin-1-yl
973	1	H	CH_2	N	CH	2-methylimidazol-1-yl
974	1	H	CH_2	N	CH	pyridin-3-yl
975	1	H	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
976	1	H	CH_2	N	CH	pyrazol-1-yl
977	1	H	CH_2	N	CH	phenyl
978	1	H	CH_2	N	CH	cyclohexyl
979	1	H	CH_2	N	CH	N,N-dimethylsulfamido
980	1	H	CH_2	N	CH	N,N-dimethylamido
981	1	H	CH_2	N	N	imidazol-1-yl
982	1	H	CH_2	N	N	morpholin-1-yl
983	1	H	CH_2	N	N	2-methylimidazol-1-yl
984	1	H	CH_2	N	N	pyridin-3-yl
985	1	H	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
986	1	H	CH_2	N	N	pyrazol-1-yl
987	1	H	CH_2	N	N	phenyl
988	1	H	CH_2	N	N	cyclohexyl
989	1	H	CH_2	N	N	N,N-dimethylsulfamido

990	1	H	CH_2	N	N	N,N-dimethylamido
991	1	H	CH_2	F	CH	imidazol-1-yl
992	1	H	CH_2	F	CH	morpholin-1-yl
993	1	H	CH_2	F	CH	2-methylimidazol-1-yl
994	1	H	CH_2	F	CH	pyridin-3-yl
995	1	H	CH_2	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
996	1	H	CH_2	F	CH	pyrazol-1-yl
997	1	H	CH_2	F	CH	phenyl
998	1	H	CH_2	F	CH	cyclohexyl
999	1	H	CH_2	F	CH	N,N-dimethylsulfamido
1000	1	H	CH_2	F	CH	N,N-dimethylamido
1001	1	H	CH_2	Cl	CH	imidazol-1-yl
1002	1	H	CH_2	Cl	CH	morpholin-1-yl
1003	1	H	CH_2	Cl	CH	2-methylimidazol-1-yl
1004	1	H	CH_2	Cl	CH	pyridin-3-yl
1005	1	H	CH_2	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1006	1	H	CH_2	Cl	CH	pyrazol-1-yl
1007	1	H	CH_2	Cl	CH	phenyl
1008	1	H	CH_2	Cl	CH	cyclohexyl
1009	1	H	CH_2	Cl	CH	N,N-dimethylsulfamido
1010	1	H	CH_2	Cl	CH	N,N-dimethylamido
1011	1	H	CH_2	Br	CH	imidazol-1-yl
1012	1	H	CH_2	Br	CH	morpholin-1-yl
1013	1	H	CH_2	Br	CH	2-methylimidazol-1-yl
1014	1	H	CH_2	Br	CH	pyridin-3-yl
1015	1	H	CH_2	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1016	1	H	CH_2	Br	CH	pyrazol-1-yl
1017	1	H	CH_2	Br	CH	phenyl
1018	1	H	CH_2	Br	CH	cyclohexyl
1019	1	H	CH_2	Br	CH	N,N-dimethylsulfamido
1020	1	H	CH_2	Br	CH	N,N-dimethylamido
1021	1	OH	bond	F	CH	pyrazol-1-yl
1022	1	OH	bond	F	CH	phenyl
1023	1	OH	bond	F	CH	cyclohexyl
1024	1	OH	bond	F	CH	N,N-dimethylsulfamido
1025	1	OH	bond	F	CH	N,N-dimethylamido
1026	1	$NHC(O)CH_3$	bond	Cl	CH	imidazol-1-yl
1027	1	$NHC(O)CH_3$	bond	Cl	CH	morpholin-1-yl
1028	1	$NHC(O)CH_3$	bond	Cl	CH	2-methylimidazol-1-yl
1029	1	$NHC(O)CH_3$	bond	Cl	CH	pyridin-3-yl
1030	1	$NHC(O)CH_3$	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1031	1	$NHSO_2CH_3$	bond	Cl	CH	pyrazol-1-yl
1032	1	$NHSO_2CH_3$	bond	Cl	CH	phenyl
1033	1	$NHSO_2CH_3$	bond	Cl	CH	cyclohexyl
1034	1	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylsulfamido
1035	1	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylamido
1036	1	OCH_3	bond	Br	CH	imidazol-1-yl
1037	1	OCH_3	bond	Br	CH	morpholin-1-yl
1038	1	OCH_3	bond	Br	CH	2-methylimidazol-1-yl

1039	1	OCH_3	bond	Br	CH	pyridin-3-yl
1040	1	OCH_3	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1041	1	$OCH_2C_6H_5$	bond	Br	CH	pyrazol-1-yl
1042	1	$OCH_2C_6H_5$	bond	Br	CH	phenyl
1043	1	$OCH_2C_6H_5$	bond	Br	CH	cyclohexyl
1044	1	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylsulfamido
1045	1	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylamido
1046	1	OH	CH_2	CH	CH	pyrazol-1-yl
1047	1	OH	CH_2	CH	CH	phenyl
1048	1	OH	CH_2	CH	CH	cyclohexyl
1049	1	OH	CH_2	CH	CH	N,N-dimethylsulfamido
1050	1	OH	CH_2	CH	CH	N,N-dimethylamido
1051	1	$NHC(O)CH_3$	CH_2	N	CH	imidazol-1-yl
1052	1	$NHC(O)CH_3$	CH_2	N	CH	morpholin-1-yl
1053	1	$NHC(O)CH_3$	CH_2	N	CH	2-methylimidazol-1-yl
1054	1	$NHC(O)CH_3$	CH_2	N	CH	pyridin-3-yl
1055	1	$NHC(O)CH_3$	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1056	1	$NHSO_2CH_3$	CH_2	N	CH	pyrazol-1-yl
1057	1	$NHSO_2CH_3$	CH_2	N	CH	phenyl
1058	1	$NHSO_2CH_3$	CH_2	N	CH	cyclohexyl
1059	1	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylsulfamido
1060	1	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylamido
1061	1	OCH_3	CH_2	N	N	imidazol-1-yl
1062	1	OCH_3	CH_2	N	N	morpholin-1-yl
1063	1	OCH_3	CH_2	N	N	2-methylimidazol-1-yl
1064	1	OCH_3	CH_2	N	N	pyridin-3-yl
1065	1	OCH_3	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
1066	1	$OCH_2C_6H_5$	CH_2	N	N	pyrazol-1-yl
1067	1	$OCH_2C_6H_5$	CH_2	N	N	phenyl
1068	1	$OCH_2C_6H_5$	CH_2	N	N	cyclohexyl
1069	1	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylsulfamido
1070	1	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylamido

Table 13



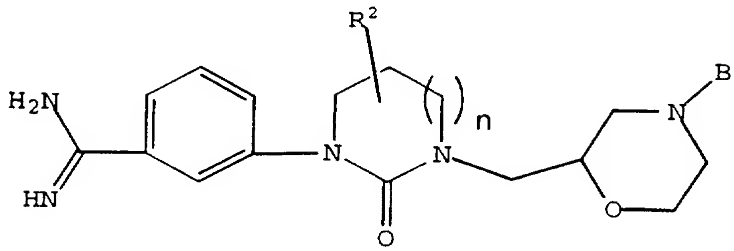
Ex.	n	R^2	Z	A^1	A^2	B
1101	2	H	bond	CH	CH	imidazol-1-yl
1102	2	H	bond	CH	CH	morpholin-1-yl
1103	2	H	bond	CH	CH	2-methylimidazol-1-yl
1104	2	H	bond	CH	CH	pyridin-3-yl
1105	2	H	bond	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1106	2	H	bond	CH	CH	pyrazol-1-yl
1107	2	H	bond	CH	CH	phenyl
1108	2	H	bond	CH	CH	cyclohexyl
1109	2	H	bond	CH	CH	N,N-dimethylsulfamido
1110	2	H	bond	CH	CH	N,N-dimethylamido
1111	2	H	bond	N	CH	imidazol-1-yl
1112	2	H	bond	N	CH	morpholin-1-yl
1113	2	H	bond	N	CH	2-methylimidazol-1-yl
1114	2	H	bond	N	CH	pyridin-3-yl
1115	2	H	bond	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1116	2	H	bond	N	CH	pyrazol-1-yl
1117	2	H	bond	N	CH	phenyl
1118	2	H	bond	N	CH	cyclohexyl
1119	2	H	bond	N	CH	N,N-dimethylsulfamido
1120	2	H	bond	N	CH	N,N-dimethylamido
1121	2	H	bond	N	N	imidazol-1-yl
1122	2	H	bond	N	N	morpholin-1-yl
1123	2	H	bond	N	N	2-methylimidazol-1-yl
1124	2	H	bond	N	N	pyridin-3-yl
1125	2	H	bond	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
1126	2	H	bond	N	N	pyrazol-1-yl
1127	2	H	bond	N	N	phenyl
1128	2	H	bond	N	N	cyclohexyl
1129	2	H	bond	N	N	N,N-dimethylsulfamido
1130	2	H	bond	N	N	N,N-dimethylamido
1131	2	H	bond	F	CH	imidazol-1-yl
1132	2	H	bond	F	CH	morpholin-1-yl
1133	2	H	bond	F	CH	2-methylimidazol-1-yl
1134	2	H	bond	F	CH	pyridin-3-yl
1135	2	H	bond	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1136	2	H	bond	F	CH	pyrazol-1-yl
1137	2	H	bond	F	CH	phenyl
1138	2	H	bond	F	CH	cyclohexyl
1139	2	H	bond	F	CH	N,N-dimethylsulfamido
1140	2	H	bond	F	CH	N,N-dimethylamido

1141	2	H	bond	Cl	CH	imidazol-1-yl
1142	2	H	bond	Cl	CH	morpholin-1-yl
1143	2	H	bond	Cl	CH	2-methylimidazol-1-yl
1144	2	H	bond	Cl	CH	pyridin-3-yl
1145	2	H	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1146	2	H	bond	Cl	CH	pyrazol-1-yl
1147	2	H	bond	Cl	CH	phenyl
1148	2	H	bond	Cl	CH	cyclohexyl
1149	2	H	bond	Cl	CH	N,N-dimethylsulfamido
1150	2	H	bond	Cl	CH	N,N-dimethylamido
1151	2	H	bond	Br	CH	imidazol-1-yl
1152	2	H	bond	Br	CH	morpholin-1-yl
1153	2	H	bond	Br	CH	2-methylimidazol-1-yl
1154	2	H	bond	Br	CH	pyridin-3-yl
1155	2	H	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1156	2	H	bond	Br	CH	pyrazol-1-yl
1157	2	H	bond	Br	CH	phenyl
1158	2	H	bond	Br	CH	cyclohexyl
1159	2	H	bond	Br	CH	N,N-dimethylsulfamido
1160	2	H	bond	Br	CH	N,N-dimethylamido
1161	2	H	CH_2	CH	CH	imidazol-1-yl
1162	2	H	CH_2	CH	CH	morpholin-1-yl
1163	2	H	CH_2	CH	CH	2-methylimidazol-1-yl
1164	2	H	CH_2	CH	CH	pyridin-3-yl
1165	2	H	CH_2	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1166	2	H	CH_2	CH	CH	pyrazol-1-yl
1167	2	H	CH_2	CH	CH	phenyl
1168	2	H	CH_2	CH	CH	cyclohexyl
1169	2	H	CH_2	CH	CH	N,N-dimethylsulfamido
1170	2	H	CH_2	CH	CH	N,N-dimethylamido
1171	2	H	CH_2	N	CH	imidazol-1-yl
1172	2	H	CH_2	N	CH	morpholin-1-yl
1173	2	H	CH_2	N	CH	2-methylimidazol-1-yl
1174	2	H	CH_2	N	CH	pyridin-3-yl
1175	2	H	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1176	2	H	CH_2	N	CH	pyrazol-1-yl
1177	2	H	CH_2	N	CH	phenyl
1178	2	H	CH_2	N	CH	cyclohexyl
1179	2	H	CH_2	N	CH	N,N-dimethylsulfamido
1180	2	H	CH_2	N	CH	N,N-dimethylamido
1181	2	H	CH_2	N	N	imidazol-1-yl
1182	2	H	CH_2	N	N	morpholin-1-yl
1183	2	H	CH_2	N	N	2-methylimidazol-1-yl
1184	2	H	CH_2	N	N	pyridin-3-yl
1185	2	H	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
1186	2	H	CH_2	N	N	pyrazol-1-yl
1187	2	H	CH_2	N	N	phenyl
1188	2	H	CH_2	N	N	cyclohexyl
1189	2	H	CH_2	N	N	N,N-dimethylsulfamido

1190	2	H	CH_2	N	N	N,N-dimethylamido
1191	2	H	CH_2	F	CH	imidazol-1-yl
1192	2	H	CH_2	F	CH	morpholin-1-yl
1193	2	H	CH_2	F	CH	2-methylimidazol-1-yl
1194	2	H	CH_2	F	CH	pyridin-3-yl
1195	2	H	CH_2	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1196	2	H	CH_2	F	CH	pyrazol-1-yl
1197	2	H	CH_2	F	CH	phenyl
1198	2	H	CH_2	F	CH	cyclohexyl
1199	2	H	CH_2	F	CH	N,N-dimethylsulfamido
1200	2	H	CH_2	F	CH	N,N-dimethylamido
1201	2	H	CH_2	Cl	CH	imidazol-1-yl
1202	2	H	CH_2	Cl	CH	morpholin-1-yl
1203	2	H	CH_2	Cl	CH	2-methylimidazol-1-yl
1204	2	H	CH_2	Cl	CH	pyridin-3-yl
1205	2	H	CH_2	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1206	2	H	CH_2	Cl	CH	pyrazol-1-yl
1207	2	H	CH_2	Cl	CH	phenyl
1208	2	H	CH_2	Cl	CH	cyclohexyl
1209	2	H	CH_2	Cl	CH	N,N-dimethylsulfamido
1210	2	H	CH_2	Cl	CH	N,N-dimethylamido
1211	2	H	CH_2	Br	CH	imidazol-1-yl
1212	2	H	CH_2	Br	CH	morpholin-1-yl
1213	2	H	CH_2	Br	CH	2-methylimidazol-1-yl
1214	2	H	CH_2	Br	CH	pyridin-3-yl
1215	2	H	CH_2	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1216	2	H	CH_2	Br	CH	pyrazol-1-yl
1217	2	H	CH_2	Br	CH	phenyl
1218	2	H	CH_2	Br	CH	cyclohexyl
1219	2	H	CH_2	Br	CH	N,N-dimethylsulfamido
1220	2	H	CH_2	Br	CH	N,N-dimethylamido
1221	2	OH	bond	F	CH	pyrazol-1-yl
1222	2	OH	bond	F	CH	phenyl
1223	2	OH	bond	F	CH	cyclohexyl
1224	2	OH	bond	F	CH	N,N-dimethylsulfamido
1225	2	OH	bond	F	CH	N,N-dimethylamido
1226	2	$NHC(O)CH_3$	bond	Cl	CH	imidazol-1-yl
1227	2	$NHC(O)CH_3$	bond	Cl	CH	morpholin-1-yl
1228	2	$NHC(O)CH_3$	bond	Cl	CH	2-methylimidazol-1-yl
1229	2	$NHC(O)CH_3$	bond	Cl	CH	pyridin-3-yl
1230	2	$NHC(O)CH_3$	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1231	2	$NHSO_2CH_3$	bond	Cl	CH	pyrazol-1-yl
1232	2	$NHSO_2CH_3$	bond	Cl	CH	phenyl
1233	2	$NHSO_2CH_3$	bond	Cl	CH	cyclohexyl
1234	2	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylsulfamido
1235	2	$NHSO_2CH_3$	bond	Cl	CH	N,N-dimethylamido
1236	2	OCH_3	bond	Br	CH	imidazol-1-yl
1237	2	OCH_3	bond	Br	CH	morpholin-1-yl
1238	2	OCH_3	bond	Br	CH	2-methylimidazol-1-yl

1239	2	OCH_3	bond	Br	CH	pyridin-3-yl
1240	2	OCH_3	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1241	2	$OCH_2C_6H_5$	bond	Br	CH	pyrazol-1-yl
1242	2	$OCH_2C_6H_5$	bond	Br	CH	phenyl
1243	2	$OCH_2C_6H_5$	bond	Br	CH	cyclohexyl
1244	2	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylsulfamido
1245	2	$OCH_2C_6H_5$	bond	Br	CH	N,N-dimethylamido
1246	2	OH	CH_2	CH	CH	pyrazol-1-yl
1247	2	OH	CH_2	CH	CH	phenyl
1248	2	OH	CH_2	CH	CH	cyclohexyl
1249	2	OH	CH_2	CH	CH	N,N-dimethylsulfamido
1250	2	OH	CH_2	CH	CH	N,N-dimethylamido
1251	2	$NHC(O)CH_3$	CH_2	N	CH	imidazol-1-yl
1252	2	$NHC(O)CH_3$	CH_2	N	CH	morpholin-1-yl
1253	2	$NHC(O)CH_3$	CH_2	N	CH	2-methylimidazol-1-yl
1254	2	$NHC(O)CH_3$	CH_2	N	CH	pyridin-3-yl
1255	2	$NHC(O)CH_3$	CH_2	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
1256	2	$NHSO_2CH_3$	CH_2	N	CH	pyrazol-1-yl
1257	2	$NHSO_2CH_3$	CH_2	N	CH	phenyl
1258	2	$NHSO_2CH_3$	CH_2	N	CH	cyclohexyl
1259	2	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylsulfamido
1260	2	$NHSO_2CH_3$	CH_2	N	CH	N,N-dimethylamido
1261	2	OCH_3	CH_2	N	N	imidazol-1-yl
1262	2	OCH_3	CH_2	N	N	morpholin-1-yl
1263	2	OCH_3	CH_2	N	N	2-methylimidazol-1-yl
1264	2	OCH_3	CH_2	N	N	pyridin-3-yl
1265	2	OCH_3	CH_2	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
1266	2	$OCH_2C_6H_5$	CH_2	N	N	pyrazol-1-yl
1267	2	$OCH_2C_6H_5$	CH_2	N	N	phenyl
1268	2	$OCH_2C_6H_5$	CH_2	N	N	cyclohexyl
1269	2	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylsulfamido
1270	2	$OCH_2C_6H_5$	CH_2	N	N	N,N-dimethylamido

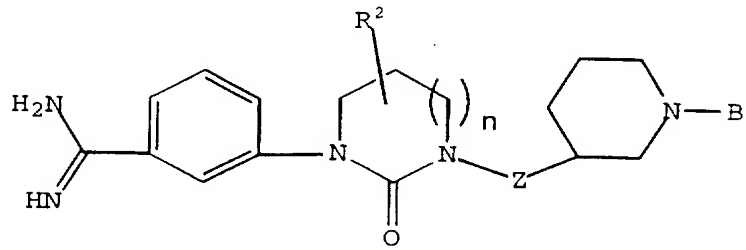
Table 14



Ex.	n	R^2	B
1301	2	H	benzoyl
1302	2	H	phenylacetyl
1303	2	H	phenylsulfonyl
1304	2	H	benzylsulfonyl
1305	2	H	picolin-2-ylsulfonyl
1306	2	H	pyridin-2-ylsulfonyl
1307	2	H	picolin-2-yl
1308	2	H	(phenyl-N-methylamino)sulfonyl
1309	2	H	(1,1-dimethyl-1-phenyl)methylsulfonyl
1310	2	H	thiophen-2-ylmethyl
1311	2	OH	benzoyl
1312	2	OH	phenylacetyl
1313	2	OH	(phenyl-N-methylamino)sulfonyl
1314	2	OH	(1,1-dimethyl-1-phenyl)methylsulfonyl
1315	2	OH	picolin-2-ylsulfonyl
1316	2	OH	pyridin-2-ylsulfonyl
1317	2	OH	picolin-2-yl
1318	2	OH	thiophen-2-ylsulfonyl
1319	2	OH	thiophen-2-ylmethylsulfonyl
1320	2	OH	thiophen-2-ylmethyl
1321	2	$NHC(O)CH_3$	(phenyl-N-methylamino)sulfonyl
1322	2	$NHC(O)CH_3$	(1,1-dimethyl-1-phenyl)methylsulfonyl
1323	2	$NHC(O)CH_3$	phenylsulfonyl
1324	2	$NHC(O)CH_3$	benzylsulfonyl
1325	2	$NHC(O)CH_3$	picolin-2-ylsulfonyl
1326	2	$NHC(O)CH_3$	pyridin-2-ylsulfonyl
1327	2	$NHC(O)CH_3$	picolin-2-yl
1328	2	$NHC(O)CH_3$	thiophen-2-ylsulfonyl
1329	2	$NHC(O)CH_3$	thiophen-2-ylmethylsulfonyl
1330	2	$NHC(O)CH_3$	thiophen-2-ylmethyl
1331	2	$NHSO_2CH_3$	benzoyl
1332	2	$NHSO_2CH_3$	phenylacetyl
1333	2	$NHSO_2CH_3$	phenylsulfonyl
1334	2	$NHSO_2CH_3$	benzylsulfonyl
1335	2	$NHSO_2CH_3$	(phenyl-N-methylamino)sulfonyl

1336	2	$NHSO_2CH_3$	(1,1-dimethyl-1-phenyl)methylsulfonyl
1337	2	$NHSO_2CH_3$	picolin-2-yl
1338	2	$NHSO_2CH_3$	thiophen-2-ylsulfonyl
1339	2	$NHSO_2CH_3$	thiophen-2-ylmethylsulfonyl
1340	2	$NHSO_2CH_3$	thiophen-2-ylmethyl

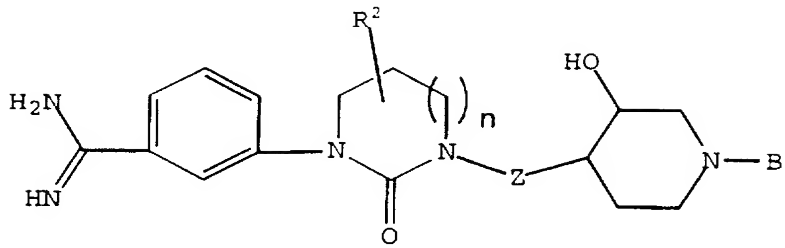
Table 15



Ex.	n	R^2	Z	B
1401	2	H	bond	benzoyl
1402	2	H	bond	phenylacetyl
1403	2	H	bond	phenylsulfonyl
1404	2	H	bond	benzylsulfonyl
1405	2	H	bond	picolin-2-ylsulfonyl
1406	2	H	bond	pyridin-2-ylsulfonyl
1407	2	H	bond	picolin-2-yl
1408	2	H	bond	(phenyl-N-methylamino)sulfonyl
1409	2	H	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1410	2	H	bond	thiophen-2-ylmethyl
1411	2	OH	bond	benzoyl
1412	2	OH	bond	phenylacetyl
1413	2	OH	bond	(phenyl-N-methylamino)sulfonyl
1414	2	OH	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1415	2	OH	bond	picolin-2-ylsulfonyl
1416	2	OH	bond	pyridin-2-ylsulfonyl
1417	2	OH	bond	picolin-2-yl
1418	2	OH	bond	thiophen-2-ylsulfonyl
1419	2	OH	bond	thiophen-2-ylmethylsulfonyl
1420	2	OH	bond	thiophen-2-ylmethyl
1421	2	$NHC(O)CH_3$	bond	(phenyl-N-methylamino)sulfonyl
1422	2	$NHC(O)CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1423	2	$NHC(O)CH_3$	bond	phenylsulfonyl
1424	2	$NHC(O)CH_3$	bond	benzylsulfonyl
1425	2	$NHC(O)CH_3$	bond	picolin-2-ylsulfonyl
1426	2	$NHC(O)CH_3$	bond	pyridin-2-ylsulfonyl
1427	2	$NHC(O)CH_3$	bond	picolin-2-yl
1428	2	$NHC(O)CH_3$	bond	thiophen-2-ylsulfonyl
1429	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethylsulfonyl
1430	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethyl
1431	2	$NHSO_2CH_3$	bond	benzoyl
1432	2	$NHSO_2CH_3$	bond	phenylacetyl
1433	2	$NHSO_2CH_3$	bond	phenylsulfonyl
1434	2	$NHSO_2CH_3$	bond	benzylsulfonyl
1435	2	$NHSO_2CH_3$	bond	(phenyl-N-methylamino)sulfonyl

1436	2	$NHSO_2CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1437	2	$NHSO_2CH_3$	bond	picolin-2-yl
1438	2	$NHSO_2CH_3$	bond	thiophen-2-ylsulfonyl
1439	2	$NHSO_2CH_3$	bond	thiophen-2-ylmethylsulfonyl
1440	2	$NHSO_2CH_3$	bond	thiophen-2-ylmethyl

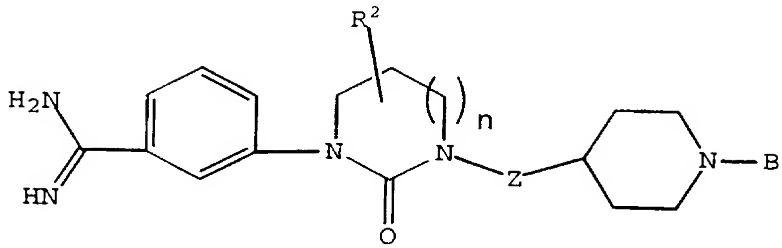
Table 16



Ex.	n	R^2	Z	B
1501	2	H	bond	benzoyl
1502	2	H	bond	phenylacetyl
1503	2	H	bond	phenylsulfonyl
1504	2	H	bond	benzylsulfonyl
1505	2	H	bond	picolin-2-ylsulfonyl
1506	2	H	bond	pyridin-2-ylsulfonyl
1507	2	H	bond	picolin-2-yl
1508	2	H	bond	(phenyl-N-methylamino)sulfonyl
1509	2	H	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1510	2	H	bond	thiophen-2-ylmethyl
1511	2	OH	bond	benzoyl
1512	2	OH	bond	phenylacetyl
1513	2	OH	bond	(phenyl-N-methylamino)sulfonyl
1514	2	OH	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1515	2	OH	bond	picolin-2-ylsulfonyl
1516	2	OH	bond	pyridin-2-ylsulfonyl
1517	2	OH	bond	picolin-2-yl
1518	2	OH	bond	thiophen-2-ylsulfonyl
1519	2	OH	bond	thiophen-2-ylmethylsulfonyl
1520	2	OH	bond	thiophen-2-ylmethyl
1521	2	$NHC(O)CH_3$	bond	(phenyl-N-methylamino)sulfonyl
1522	2	$NHC(O)CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1523	2	$NHC(O)CH_3$	bond	phenylsulfonyl
1524	2	$NHC(O)CH_3$	bond	benzylsulfonyl
1525	2	$NHC(O)CH_3$	bond	picolin-2-ylsulfonyl
1526	2	$NHC(O)CH_3$	bond	pyridin-2-ylsulfonyl
1527	2	$NHC(O)CH_3$	bond	picolin-2-yl
1528	2	$NHC(O)CH_3$	bond	thiophen-2-ylsulfonyl
1529	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethylsulfonyl
1530	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethyl
1531	2	$NHSO_2CH_3$	bond	benzoyl
1532	2	$NHSO_2CH_3$	bond	phenylacetyl
1533	2	$NHSO_2CH_3$	bond	phenylsulfonyl
1534	2	$NHSO_2CH_3$	bond	benzylsulfonyl
1535	2	$NHSO_2CH_3$	bond	(phenyl-N-methylamino)sulfonyl

1536	2	$NHSO_2CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1537	2	$NHSO_2CH_3$	bond	picolin-2-yl
1538	2	$NHSO_2CH_3$	bond	thiophen-2-ylsulfonyl
1539	2	$NHSO_2CH_3$	bond	thiophen-2-ylmethylsulfonyl
1540	2	$NHSO_2CH_3$	bond	thiophen-2-ylmethyl

Table 17

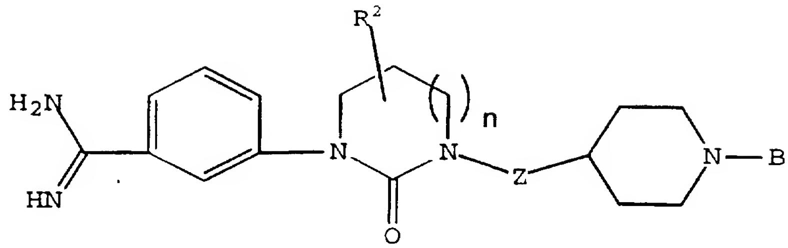


Ex.	n	R^2	Z	B
1601	2	H	bond	picolin-2-ylsulfonyl
1602	2	H	bond	pyridin-2-ylsulfonyl
1603	2	H	bond	picolin-2-yl
1604	2	H	bond	thiophen-2-ylsulfonyl
1605	2	H	bond	thiophen-2-ylmethylsulfonyl
1606	2	H	bond	thiophen-2-ylmethyl
1607	2	H	bond	4-fluorophenylsulfonyl
1608	2	H	bond	4-fluorobenzylsulfonyl
1609	2	H	bond	phenylsulfonyl
1610	2	H	bond	benzylsulfonyl
1611	2	H	bond	(phenyl-N-methylamino)sulfonyl
1612	2	H	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1613	2	OH	bond	picolin-2-ylsulfonyl
1614	2	OH	bond	pyridin-2-ylsulfonyl
1615	2	OH	bond	picolin-2-yl
1616	2	OH	bond	thiophen-2-ylsulfonyl
1617	2	OH	bond	thiophen-2-ylmethylsulfonyl
1618	2	OH	bond	thiophen-2-ylmethyl
1619	2	OH	bond	4-fluorophenylsulfonyl
1620	2	OH	bond	4-fluorobenzylsulfonyl
1621	2	OH	bond	(phenyl-N-methylamino)sulfonyl
1622	2	OH	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1623	2	OCH_3	bond	picolin-2-ylsulfonyl
1624	2	OCH_3	bond	pyridin-2-ylsulfonyl
1625	2	OCH_3	bond	picolin-2-yl
1626	2	OCH_3	bond	thiophen-2-ylsulfonyl
1627	2	OCH_3	bond	thiophen-2-ylmethylsulfonyl
1628	2	OCH_3	bond	thiophen-2-ylmethyl
1629	2	OCH_3	bond	(phenyl-N-methylamino)sulfonyl
1630	2	OCH_3	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1631	2	OCH_3	bond	phenylsulfonyl
1632	2	OCH_3	bond	benzylsulfonyl
1633	2	$OCH_2C_6H_5$	bond	picolin-2-ylsulfonyl
1634	2	$OCH_2C_6H_5$	bond	pyridin-2-ylsulfonyl
1635	2	$OCH_2C_6H_5$	bond	picolin-2-yl
1636	2	$OCH_2C_6H_5$	bond	thiophen-2-ylsulfonyl

1637	2	$OCH_2C_6H_5$	bond	(phenyl-N-methylamino)sulfonyl
1638	2	$OCH_2C_6H_5$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1639	2	$OCH_2C_6H_5$	bond	4-fluorophenylsulfonyl
1640	2	$OCH_2C_6H_5$	bond	4-fluorobenzylsulfonyl
1641	2	$OCH_2C_6H_5$	bond	phenylsulfonyl
1642	2	$OCH_2C_6H_5$	bond	benzylsulfonyl
1643	2	$NHC(O)CH_3$	bond	picolin-2-ylsulfonyl
1644	2	$NHC(O)CH_3$	bond	pyridin-2-ylsulfonyl
1645	2	$NHC(O)CH_3$	bond	(phenyl-N-methylamino)sulfonyl
1646	2	$NHC(O)CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1647	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethylsulfonyl
1648	2	$NHC(O)CH_3$	bond	thiophen-2-ylmethyl
1649	2	$NHC(O)CH_3$	bond	4-fluorophenylsulfonyl
1650	2	$NHC(O)CH_3$	bond	4-fluorobenzylsulfonyl
1651	2	$NHC(O)CH_3$	bond	phenylsulfonyl
1652	2	$NHC(O)CH_3$	bond	benzylsulfonyl
1653	2	$NHC(O)OCH_3$	bond	(phenyl-N-methylamino)sulfonyl
1654	2	$NHC(O)OCH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1655	2	$NHC(O)OCH_3$	bond	picolin-2-yl
1656	2	$NHC(O)OCH_3$	bond	thiophen-2-ylsulfonyl
1657	2	$NHC(O)OCH_3$	bond	thiophen-2-ylmethylsulfonyl
1658	2	$NHC(O)OCH_3$	bond	thiophen-2-ylmethyl
1659	2	$NHC(O)OCH_3$	bond	4-fluorophenylsulfonyl
1660	2	$NHC(O)OCH_3$	bond	4-fluorobenzylsulfonyl
1661	2	$NHC(O)OCH_3$	bond	phenylsulfonyl
1662	2	$NHC(O)OCH_3$	bond	benzylsulfonyl
1663	2	$NHC(O)NHCH_3$	bond	picolin-2-ylsulfonyl
1664	2	$NHC(O)NHCH_3$	bond	pyridin-2-ylsulfonyl
1665	2	$NHC(O)NHCH_3$	bond	picolin-2-yl
1666	2	$NHC(O)NHCH_3$	bond	thiophen-2-ylsulfonyl
1667	2	$NHC(O)NHCH_3$	bond	thiophen-2-ylmethylsulfonyl
1668	2	$NHC(O)NHCH_3$	bond	thiophen-2-ylmethyl
1669	2	$NHC(O)NHCH_3$	bond	4-fluorophenylsulfonyl
1670	2	$NHC(O)NHCH_3$	bond	4-fluorobenzylsulfonyl
1671	2	$NHC(O)NHCH_3$	bond	(phenyl-N-methylamino)sulfonyl
1672	2	$NHC(O)NHCH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1673	2	$NHC(O)C_6H_5$	bond	picolin-2-ylsulfonyl
1674	2	$NHC(O)C_6H_5$	bond	pyridin-2-ylsulfonyl
1675	2	$NHC(O)C_6H_5$	bond	picolin-2-yl
1676	2	$NHC(O)C_6H_5$	bond	thiophen-2-ylsulfonyl
1677	2	$NHC(O)C_6H_5$	bond	thiophen-2-ylmethylsulfonyl
1678	2	$NHC(O)C_6H_5$	bond	thiophen-2-ylmethyl
1679	2	$NHC(O)C_6H_5$	bond	(phenyl-N-methylamino)sulfonyl
1680	2	$NHC(O)C_6H_5$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl

1681	2	$NHC(O)C_6H_5$	bond	phenylsulfonyl
1682	2	$NHC(O)C_6H_5$	bond	benzylsulfonyl
1683	2	$NHSO_2CH_3$	bond	picolin-2-ylsulfonyl
1684	2	$NHSO_2CH_3$	bond	pyridin-2-ylsulfonyl
1685	2	$NHSO_2CH_3$	bond	picolin-2-yl
1686	2	$NHSO_2CH_3$	bond	thiophen-2-ylsulfonyl
1687	2	$NHSO_2CH_3$	bond	(phenyl-N-methylamino)sulfonyl
1688	2	$NHSO_2CH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1689	2	$NHSO_2CH_3$	bond	4-fluorophenylsulfonyl
1690	2	$NHSO_2CH_3$	bond	4-fluorobenzylsulfonyl
1691	2	$NHSO_2CH_3$	bond	phenylsulfonyl
1692	2	$NHSO_2CH_3$	bond	benzylsulfonyl
1693	2	$NHSO_2NHCH_3$	bond	picolin-2-ylsulfonyl
1694	2	$NHSO_2NHCH_3$	bond	pyridin-2-ylsulfonyl
1695	2	$NHSO_2NHCH_3$	bond	(phenyl-N-methylamino)sulfonyl
1696	2	$NHSO_2NHCH_3$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1697	2	$NHSO_2NHCH_3$	bond	thiophen-2-ylmethylsulfonyl
1698	2	$NHSO_2NHCH_3$	bond	thiophen-2-ylmethyl
1699	2	$NHSO_2NHCH_3$	bond	4-fluorophenylsulfonyl
1700	2	$NHSO_2NHCH_3$	bond	4-fluorobenzylsulfonyl
1701	2	$NHSO_2NHCH_3$	bond	phenylsulfonyl
1702	2	$NHSO_2NHCH_3$	bond	benzylsulfonyl
1703	2	$NHSO_2C_6H_5$	bond	(phenyl-N-methylamino)sulfonyl
1704	2	$NHSO_2C_6H_5$	bond	(1,1-dimethyl-1-phenyl)methylsulfonyl
1705	2	$NHSO_2C_6H_5$	bond	picolin-2-yl
1706	2	$NHSO_2C_6H_5$	bond	thiophen-2-ylsulfonyl
1707	2	$NHSO_2C_6H_5$	bond	thiophen-2-ylmethylsulfonyl
1708	2	$NHSO_2C_6H_5$	bond	thiophen-2-ylmethyl
1709	2	$NHSO_2C_6H_5$	bond	4-fluorophenylsulfonyl
1710	2	$NHSO_2C_6H_5$	bond	4-fluorobenzylsulfonyl
1711	2	$NHSO_2C_6H_5$	bond	phenylsulfonyl
1712	2	$NHSO_2C_6H_5$	bond	benzylsulfonyl

Table 18

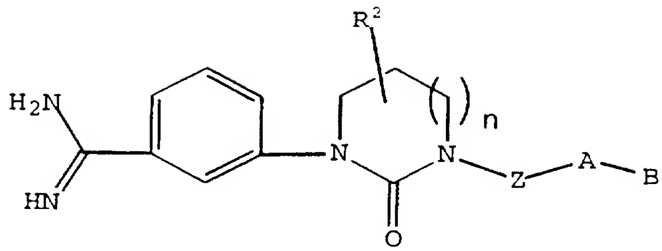


Ex.	n	R^2	Z	B
1801	2	H	CH_2	picolin-2-ylsulfonyl
1802	2	H	CH_2	pyridin-2-ylsulfonyl
1803	2	H	CH_2	picolin-2-yl
1804	2	H	CH_2	thiophen-2-ylsulfonyl
1805	2	H	CH_2	thiophen-2-ylmethylsulfonyl
1806	2	H	CH_2	thiophen-2-ylmethyl
1807	2	H	CH_2	4-fluorophenylsulfonyl
1808	2	H	CH_2	4-fluorobenzylsulfonyl
1809	2	H	CH_2	(phenyl-N-methylamino)sulfonyl
1810	2	H	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1811	2	OH	CH_2	picolin-2-ylsulfonyl
1812	2	OH	CH_2	pyridin-2-ylsulfonyl
1813	2	OH	CH_2	picolin-2-yl
1814	2	OH	CH_2	thiophen-2-ylsulfonyl
1815	2	OH	CH_2	thiophen-2-ylmethylsulfonyl
1816	2	OH	CH_2	thiophen-2-ylmethyl
1817	2	OH	CH_2	4-fluorophenylsulfonyl
1818	2	OH	CH_2	4-fluorobenzylsulfonyl
1819	2	OH	CH_2	(phenyl-N-methylamino)sulfonyl
1820	2	OH	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1821	2	OCH_3	CH_2	picolin-2-ylsulfonyl
1822	2	OCH_3	CH_2	pyridin-2-ylsulfonyl
1823	2	OCH_3	CH_2	picolin-2-yl
1824	2	OCH_3	CH_2	thiophen-2-ylsulfonyl
1825	2	OCH_3	CH_2	thiophen-2-ylmethylsulfonyl
1826	2	OCH_3	CH_2	thiophen-2-ylmethyl
1827	2	OCH_3	CH_2	(phenyl-N-methylamino)sulfonyl
1828	2	OCH_3	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1829	2	OCH_3	CH_2	phenylsulfonyl
1830	2	OCH_3	CH_2	benzylsulfonyl
1831	2	$OCH_2C_6H_5$	CH_2	picolin-2-ylsulfonyl
1832	2	$OCH_2C_6H_5$	CH_2	pyridin-2-ylsulfonyl
1833	2	$OCH_2C_6H_5$	CH_2	picolin-2-yl
1834	2	$OCH_2C_6H_5$	CH_2	thiophen-2-ylsulfonyl

1835	2	$OCH_2C_6H_5$	CH_2	(phenyl-N-methylamino)sulfonyl
1836	2	$OCH_2C_6H_5$	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1837	2	$OCH_2C_6H_5$	CH_2	4-fluorophenylsulfonyl
1838	2	$OCH_2C_6H_5$	CH_2	4-fluorobenzylsulfonyl
1839	2	$OCH_2C_6H_5$	CH_2	phenylsulfonyl
1840	2	$OCH_2C_6H_5$	CH_2	benzylsulfonyl
1841	2	NHC(O)CH_3	CH_2	picolin-2-ylsulfonyl
1842	2	NHC(O)CH_3	CH_2	pyridin-2-ylsulfonyl
1843	2	NHC(O)CH_3	CH_2	(phenyl-N-methylamino)sulfonyl
1844	2	NHC(O)CH_3	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1845	2	NHC(O)CH_3	CH_2	thiophen-2-ylmethylsulfonyl
1846	2	NHC(O)CH_3	CH_2	thiophen-2-ylmethyl
1847	2	NHC(O)CH_3	CH_2	4-fluorophenylsulfonyl
1848	2	NHC(O)CH_3	CH_2	4-fluorobenzylsulfonyl
1849	2	NHC(O)CH_3	CH_2	phenylsulfonyl
1850	2	NHC(O)CH_3	CH_2	benzylsulfonyl
1851	2	NHC(O)OCH_3	CH_2	(phenyl-N-methylamino)sulfonyl
1852	2	NHC(O)OCH_3	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1853	2	NHC(O)OCH_3	CH_2	picolin-2-yl
1854	2	NHC(O)OCH_3	CH_2	thiophen-2-ylsulfonyl
1855	2	NHC(O)OCH_3	CH_2	thiophen-2-ylmethylsulfonyl
1856	2	NHC(O)OCH_3	CH_2	thiophen-2-ylmethyl
1857	2	NHC(O)OCH_3	CH_2	4-fluorophenylsulfonyl
1858	2	NHC(O)OCH_3	CH_2	4-fluorobenzylsulfonyl
1859	2	NHC(O)OCH_3	CH_2	phenylsulfonyl
1860	2	NHC(O)OCH_3	CH_2	benzylsulfonyl
1861	2	NHC(O)$NHCH_3$	CH_2	picolin-2-ylsulfonyl
1862	2	NHC(O)$NHCH_3$	CH_2	pyridin-2-ylsulfonyl
1863	2	NHC(O)$NHCH_3$	CH_2	picolin-2-yl
1864	2	NHC(O)$NHCH_3$	CH_2	thiophen-2-ylsulfonyl
1865	2	NHC(O)$NHCH_3$	CH_2	thiophen-2-ylmethylsulfonyl
1866	2	NHC(O)$NHCH_3$	CH_2	thiophen-2-ylmethyl
1867	2	NHC(O)$NHCH_3$	CH_2	4-fluorophenylsulfonyl
1868	2	NHC(O)$NHCH_3$	CH_2	4-fluorobenzylsulfonyl
1869	2	NHC(O)$NHCH_3$	CH_2	(phenyl-N-methylamino)sulfonyl
1870	2	NHC(O)$NHCH_3$	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1871	2	NHC(O)C_6H_5	CH_2	picolin-2-ylsulfonyl
1872	2	NHC(O)C_6H_5	CH_2	pyridin-2-ylsulfonyl
1873	2	NHC(O)C_6H_5	CH_2	picolin-2-yl
1874	2	NHC(O)C_6H_5	CH_2	thiophen-2-ylsulfonyl
1875	2	NHC(O)C_6H_5	CH_2	thiophen-2-ylmethylsulfonyl
1876	2	NHC(O)C_6H_5	CH_2	thiophen-2-ylmethyl
1877	2	NHC(O)C_6H_5	CH_2	(phenyl-N-methylamino)sulfonyl
1878	2	NHC(O)C_6H_5	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl

1879	2	$NHC(O)C_6H_5$	CH_2	phenylsulfonyl
1880	2	$NHC(O)C_6H_5$	CH_2	benzylsulfonyl
1881	2	$NHSO_2CH_3$	CH_2	picolin-2-ylsulfonyl
1882	2	$NHSO_2CH_3$	CH_2	pyridin-2-ylsulfonyl
1883	2	$NHSO_2CH_3$	CH_2	picolin-2-yl
1884	2	$NHSO_2CH_3$	CH_2	thiophen-2-ylsulfonyl
1885	2	$NHSO_2CH_3$	CH_2	(phenyl-N-methylamino)sulfonyl
1886	2	$NHSO_2CH_3$	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1887	2	$NHSO_2CH_3$	CH_2	4-fluorophenylsulfonyl
1888	2	$NHSO_2CH_3$	CH_2	4-fluorobenzylsulfonyl
1889	2	$NHSO_2CH_3$	CH_2	phenylsulfonyl
1890	2	$NHSO_2CH_3$	CH_2	benzylsulfonyl
1891	2	$NHSO_2NHCH_3$	CH_2	picolin-2-ylsulfonyl
1892	2	$NHSO_2NHCH_3$	CH_2	pyridin-2-ylsulfonyl
1893	2	$NHSO_2NHCH_3$	CH_2	(phenyl-N-methylamino)sulfonyl
1894	2	$NHSO_2NHCH_3$	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1895	2	$NHSO_2NHCH_3$	CH_2	thiophen-2-ylmethylsulfonyl
1896	2	$NHSO_2NHCH_3$	CH_2	thiophen-2-ylmethyl
1897	2	$NHSO_2NHCH_3$	CH_2	4-fluorophenylsulfonyl
1898	2	$NHSO_2NHCH_3$	CH_2	4-fluorobenzylsulfonyl
1899	2	$NHSO_2NHCH_3$	CH_2	phenylsulfonyl
1900	2	$NHSO_2NHCH_3$	CH_2	benzylsulfonyl
1901	2	$NHSO_2C_6H_5$	CH_2	(phenyl-N-methylamino)sulfonyl
1902	2	$NHSO_2C_6H_5$	CH_2	(1,1-dimethyl-1-phenyl)methylsulfonyl
1903	2	$NHSO_2C_6H_5$	CH_2	picolin-2-yl
1904	2	$NHSO_2C_6H_5$	CH_2	thiophen-2-ylsulfonyl
1905	2	$NHSO_2C_6H_5$	CH_2	thiophen-2-ylmethylsulfonyl
1906	2	$NHSO_2C_6H_5$	CH_2	thiophen-2-ylmethyl
1907	2	$NHSO_2C_6H_5$	CH_2	4-fluorophenylsulfonyl
1908	2	$NHSO_2C_6H_5$	CH_2	4-fluorobenzylsulfonyl
1909	2	$NHSO_2C_6H_5$	CH_2	phenylsulfonyl
1910	2	$NHSO_2C_6H_5$	CH_2	benzylsulfonyl

Table 19

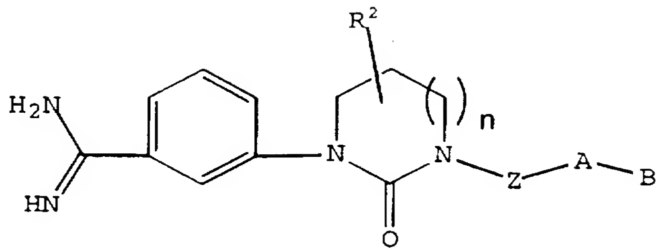


Ex.	n	R^2	Z	A*	B*
2001	0	H	$(CH_2)_2O$	phenyl	amino
2002	0	H	$(CH_2)_2O$	phenyl	amidino
2003	0	H	$(CH_2)_2O$	phenyl	guanidino
2004	0	H	$(CH_2)_2O$	phenyl	benzyl
2005	0	H	$(CH_2)_2C(O)$	phenyl	phenyl
2006	0	H	$(CH_2)_2C(O)$	phenyl	cyclohexyl
2007	0	H	$(CH_2)_2C(O)$	phenyl	4-pyridyl
2008	0	H	$(CH_2)_2C(O)$	phenyl	2-furanyl
2009	0	H	$(CH_2)_2C(O)O$	phenyl	piperidinyl
2010	0	H	$(CH_2)_2C(O)O$	phenyl	phenethyl
2011	0	H	$(CH_2)_2C(O)O$	phenyl	phenylcarbonyl
2012	0	H	$(CH_2)_2C(O)O$	phenyl	2-aminophenyl-carbonyl
2013	0	H	$(CH_2)_2C(O)NH$	phenyl	benzylcarbonyl
2014	0	H	$(CH_2)_2C(O)NH$	phenyl	4-acetamidophenyl-methanecarbonyl
2015	0	H	$(CH_2)_2C(O)NH$	phenyl	phenylsulfonyl
2016	0	H	$(CH_2)_2C(O)NH$	phenyl	4-amidinophenyl-sulfonyl
2017	0	H	$(CH_2)_2NHC(O)NH$	phenyl	benzylsulfonyl
2018	0	H	$(CH_2)_2NHC(O)NH$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2019	0	H	$(CH_2)_2NHC(O)NH$	phenyl	phenylsulfonamide
2020	0	H	$(CH_2)_2NHC(O)NH$	phenyl	4-acetamidophenyl-sulfonamide
2021	0	H	$(CH_2)_2S(O)_2NH$	phenyl	phenylcarbamide
2022	0	H	$(CH_2)_2S(O)_2NH$	phenyl	2-aminophenyl-carbamide
2023	0	H	$(CH_2)_2S(O)_2NH$	phenyl	benzylamine
2024	0	H	$(CH_2)_2S(O)_2NH$	phenyl	4-amidinophenyl-methaneamine
2025	0	H	$(CH_2)_2OCH_2$	phenyl	amino
2026	0	H	$(CH_2)_2OCH_2$	phenyl	amidino
2027	0	H	$(CH_2)_2OCH_2$	phenyl	guanidino
2028	0	H	$(CH_2)_2OCH_2$	phenyl	benzyl
2029	0	H	$(CH_2)_2C(O)CH_2$	phenyl	phenyl
2030	0	H	$(CH_2)_2C(O)CH_2$	phenyl	cyclohexyl
2031	0	H	$(CH_2)_2C(O)CH_2$	phenyl	4-pyridyl
2032	0	H	$(CH_2)_2C(O)CH_2$	phenyl	2-furanyl
2033	0	H	$(CH_2)_2C(O)OCH_2$	phenyl	piperidinyl

2034	0	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenethyl
2035	0	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenylcarbonyl
2036	0	H	$(CH_2)_2C(O)OCH_2$	phenyl	2-aminophenyl-carbonyl
2037	0	H	$(CH_2)_2C(O)NHCH_2$	phenyl	benzylcarbonyl
2038	0	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-acetamidophenyl-methanecarbonyl
2039	0	H	$(CH_2)_2C(O)NHCH_2$	phenyl	phenylsulfonyl
2040	0	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-amidinophenyl-sulfonyl
2041	0	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	benzylsulfonyl
2042	0	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2043	0	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	phenylsulfonamide
2044	0	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-acetamidophenyl-sulfonamide
2045	0	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	phenylcarbamide
2046	0	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	2-aminophenyl-carbamide
2047	0	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	benzylamine
2048	0	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	4-amidinophenyl-methaneamine

*B is substituted para to Z on A.

Table 20

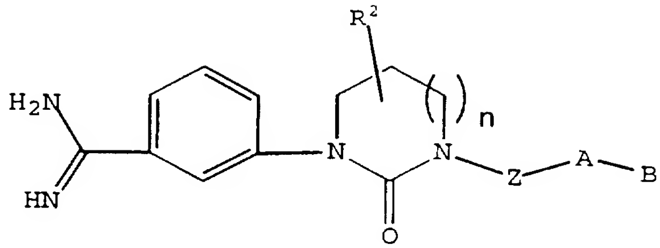


Ex.	n	R^2	Z	A*	B*
2101	1	H	$(CH_2)_2O$	phenyl	amino
2102	1	H	$(CH_2)_2O$	phenyl	amidino
2103	1	H	$(CH_2)_2O$	phenyl	guanidino
2104	1	H	$(CH_2)_2O$	phenyl	benzyl
2105	1	H	$(CH_2)_2C(O)$	phenyl	phenyl
2106	1	H	$(CH_2)_2C(O)$	phenyl	cyclohexyl
2107	1	H	$(CH_2)_2C(O)$	phenyl	4-pyridyl
2108	1	H	$(CH_2)_2C(O)$	phenyl	2-furanyl
2109	1	H	$(CH_2)_2C(O)O$	phenyl	piperidinyl
2110	1	H	$(CH_2)_2C(O)O$	phenyl	phenethyl
2111	1	H	$(CH_2)_2C(O)O$	phenyl	phenylcarbonyl
2112	1	H	$(CH_2)_2C(O)O$	phenyl	2-aminophenyl-carbonyl
2113	1	H	$(CH_2)_2C(O)NH$	phenyl	benzylcarbonyl
2114	1	H	$(CH_2)_2C(O)NH$	phenyl	4-acetamidophenyl-methanecarbonyl
2115	1	H	$(CH_2)_2C(O)NH$	phenyl	phenylsulfonyl
2116	1	H	$(CH_2)_2C(O)NH$	phenyl	4-amidinophenyl-sulfonyl
2117	1	H	$(CH_2)_2NHC(O)NH$	phenyl	benzylsulfonyl
2118	1	H	$(CH_2)_2NHC(O)NH$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2119	1	H	$(CH_2)_2NHC(O)NH$	phenyl	phenylsulfonamide
2120	1	H	$(CH_2)_2NHC(O)NH$	phenyl	4-acetamidophenyl-sulfonamide
2121	1	H	$(CH_2)_2S(O)_2NH$	phenyl	phenylcarbamide
2122	1	H	$(CH_2)_2S(O)_2NH$	phenyl	2-aminophenyl-carbamide
2123	1	H	$(CH_2)_2S(O)_2NH$	phenyl	benzylamine
2124	1	H	$(CH_2)_2S(O)_2NH$	phenyl	4-amidinophenyl-methaneamine
2125	1	H	$(CH_2)_2OCH_2$	phenyl	amino
2126	1	H	$(CH_2)_2OCH_2$	phenyl	amidino
2127	1	H	$(CH_2)_2OCH_2$	phenyl	guanidino
2128	1	H	$(CH_2)_2OCH_2$	phenyl	benzyl
2129	1	H	$(CH_2)_2C(O)CH_2$	phenyl	phenyl
2130	1	H	$(CH_2)_2C(O)CH_2$	phenyl	cyclohexyl
2131	1	H	$(CH_2)_2C(O)CH_2$	phenyl	4-pyridyl
2132	1	H	$(CH_2)_2C(O)CH_2$	phenyl	2-furanyl
2133	1	H	$(CH_2)_2C(O)OCH_2$	phenyl	piperidinyl

2134	1	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenethyl
2135	1	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenylcarbonyl
2136	1	H	$(CH_2)_2C(O)OCH_2$	phenyl	2-aminophenyl-carbonyl
2137	1	H	$(CH_2)_2C(O)NHCH_2$	phenyl	benzylcarbonyl
2138	1	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-acetamidophenyl-methanecarbonyl
2139	1	H	$(CH_2)_2C(O)NHCH_2$	phenyl	phenylsulfonyl
2140	1	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-amidinophenyl-sulfonyl
2141	1	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	benzylsulfonyl
2142	1	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2143	1	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	phenylsulfonamide
2144	1	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-acetamidophenyl-sulfonamide
2145	1	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	phenylcarbamide
2146	1	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	2-aminophenyl-carbamide
2147	1	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	benzylamine
2148	1	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	4-amidinophenyl-methaneamine

*B is substituted para to Z on A.

Table 21

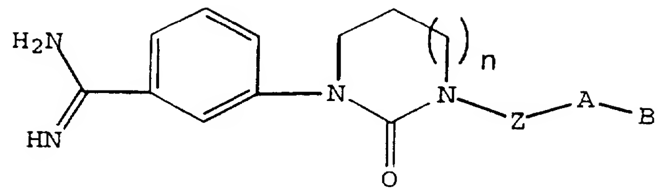


Ex.	n	R^2	Z	A*	B*
2201	2	H	$(CH_2)_2O$	phenyl	amino
2202	2	H	$(CH_2)_2O$	phenyl	amidino
2203	2	H	$(CH_2)_2O$	phenyl	guanidino
2204	2	H	$(CH_2)_2O$	phenyl	benzyl
2205	2	H	$(CH_2)_2C(O)$	phenyl	phenyl
2206	2	H	$(CH_2)_2C(O)$	phenyl	cyclohexyl
2207	2	H	$(CH_2)_2C(O)$	phenyl	4-pyridyl
2208	2	H	$(CH_2)_2C(O)$	phenyl	2-furanyl
2209	2	H	$(CH_2)_2C(O)O$	phenyl	piperidinyl
2210	2	H	$(CH_2)_2C(O)O$	phenyl	phenethyl
2211	2	H	$(CH_2)_2C(O)O$	phenyl	phenylcarbonyl
2212	2	H	$(CH_2)_2C(O)O$	phenyl	2-aminophenyl-carbonyl
2213	2	H	$(CH_2)_2C(O)NH$	phenyl	benzylcarbonyl
2214	2	H	$(CH_2)_2C(O)NH$	phenyl	4-acetamidophenyl-methanecarbonyl
2215	2	H	$(CH_2)_2C(O)NH$	phenyl	phenylsulfonyl
2216	2	H	$(CH_2)_2C(O)NH$	phenyl	4-amidinophenyl-sulfonyl
2217	2	H	$(CH_2)_2NHC(O)NH$	phenyl	benzylsulfonyl
2218	2	H	$(CH_2)_2NHC(O)NH$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2219	2	H	$(CH_2)_2NHC(O)NH$	phenyl	phenylsulfonamide
2220	2	H	$(CH_2)_2NHC(O)NH$	phenyl	4-acetamidophenyl-sulfonamide
2221	2	H	$(CH_2)_2S(O)_2NH$	phenyl	phenylcarbamide
2222	2	H	$(CH_2)_2S(O)_2NH$	phenyl	2-aminophenyl-carbamide
2223	2	H	$(CH_2)_2S(O)_2NH$	phenyl	benzylamine
2224	2	H	$(CH_2)_2S(O)_2NH$	phenyl	4-amidinophenyl-methaneamine
2225	2	H	$(CH_2)_2OCH_2$	phenyl	amino
2226	2	H	$(CH_2)_2OCH_2$	phenyl	amidino
2227	2	H	$(CH_2)_2OCH_2$	phenyl	guanidino
2228	2	H	$(CH_2)_2OCH_2$	phenyl	benzyl
2229	2	H	$(CH_2)_2C(O)CH_2$	phenyl	phenyl
2230	2	H	$(CH_2)_2C(O)CH_2$	phenyl	cyclohexyl
2231	2	H	$(CH_2)_2C(O)CH_2$	phenyl	4-pyridyl
2232	2	H	$(CH_2)_2C(O)CH_2$	phenyl	2-furanyl
2233	2	H	$(CH_2)_2C(O)OCH_2$	phenyl	piperidinyl

2234	2	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenethyl
2235	2	H	$(CH_2)_2C(O)OCH_2$	phenyl	phenylcarbonyl
2236	2	H	$(CH_2)_2C(O)OCH_2$	phenyl	2-aminophenyl-carbonyl
2237	2	H	$(CH_2)_2C(O)NHCH_2$	phenyl	benzylcarbonyl
2238	2	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-acetamidophenyl-methanecarbonyl
2239	2	H	$(CH_2)_2C(O)NHCH_2$	phenyl	phenylsulfonyl
2240	2	H	$(CH_2)_2C(O)NHCH_2$	phenyl	4-amidinophenyl-sulfonyl
2241	2	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	benzylsulfonyl
2242	2	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-methoxycarbonyl-phenylmethane-sulfonyl
2243	2	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	phenylsulfonamide
2244	2	H	$(CH_2)_2NHC(O)NHCH_2$	phenyl	4-acetamidophenyl-sulfonamide
2245	2	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	phenylcarbamide
2246	2	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	2-aminophenyl-carbamide
2247	2	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	benzylamine
2248	2	H	$(CH_2)_2S(O)_2NHCH_2$	phenyl	4-amidinophenyl-methaneamine

*B is substituted para to Z on A.

Table 22

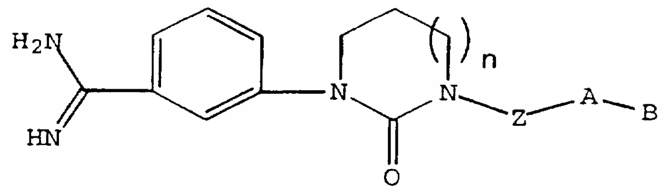


Ex.	n	Z	A*	B*
2301	0	$(CH_2)_2O$	2-fluorophenyl	imidazol-1-yl
2302	0	$(CH_2)_2O$	2-chlorophenyl	N,N-dimethylamido
2303	0	$(CH_2)_2O$	2-bromophenyl	morpholin-1-yl
2304	0	$(CH_2)_2O$	2-pyridyl	2-methylindazol-1-yl
2305	0	$(CH_2)_2O$	2-pyrimidinyl	N,N-dimethylsulfamido
2306	0	$(CH_2)_2C(O)$	2-fluorophenyl	pyridin-3-yl
2307	0	$(CH_2)_2C(O)$	2-chlorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2308	0	$(CH_2)_2C(O)$	2-bromophenyl	pyrazol-1-yl
2309	0	$(CH_2)_2C(O)$	2-pyridyl	cyclohexyl
2310	0	$(CH_2)_2C(O)O$	2-pyrimidinyl	imidazol-1-yl
2311	0	$(CH_2)_2C(O)O$	2-fluorophenyl	N,N-dimethylamido
2312	0	$(CH_2)_2C(O)O$	2-chlorophenyl	morpholin-1-yl
2313	0	$(CH_2)_2C(O)O$	2-bromophenyl	2-methylindazol-1-yl
2314	0	$(CH_2)_2C(O)NH$	2-pyridyl	N,N-dimethylsulfamido
2315	0	$(CH_2)_2C(O)NH$	2-pyrimidinyl	pyridin-3-yl
2316	0	$(CH_2)_2C(O)NH$	2-fluorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2317	0	$(CH_2)_2C(O)NH$	2-chlorophenyl	pyrazol-1-yl
2318	0	$(CH_2)_2C(O)NH$	2-bromophenyl	cyclohexyl
2319	0	$(CH_2)_2NHC(O)NH$	2-pyridyl	imidazol-1-yl
2320	0	$(CH_2)_2NHC(O)NH$	2-pyrimidinyl	N,N-dimethylamido
2321	0	$(CH_2)_2NHC(O)NH$	2-fluorophenyl	morpholin-1-yl
2322	0	$(CH_2)_2NHC(O)NH$	2-chlorophenyl	2-methylindazol-1-yl
2323	0	$(CH_2)_2S(O)_2NH$	2-bromophenyl	N,N-dimethylsulfamido
2324	0	$(CH_2)_2S(O)_2NH$	2-pyridyl	pyridin-3-yl
2325	0	$(CH_2)_2S(O)_2NH$	2-pyrimidinyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2326	0	$(CH_2)_2S(O)_2NH$	2-fluorophenyl	pyrazol-1-yl
2327	0	$(CH_2)_2S(O)_2NH$	2-chlorophenyl	cyclohexyl
2328	0	$(CH_2)_2OCH_2$	2-bromophenyl	imidazol-1-yl
2329	0	$(CH_2)_2OCH_2$	2-pyridyl	N,N-dimethylamido
2330	0	$(CH_2)_2OCH_2$	2-pyrimidinyl	morpholin-1-yl
2331	0	$(CH_2)_2OCH_2$	2-fluorophenyl	2-methylindazol-1-yl
2332	0	$(CH_2)_2OCH_2$	2-chlorophenyl	N,N-dimethylsulfamido
2333	0	$(CH_2)_2C(O)CH_2$	2-bromophenyl	pyridin-3-yl
2334	0	$(CH_2)_2C(O)CH_2$	2-pyridyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2335	0	$(CH_2)_2C(O)CH_2$	2-pyrimidinyl	pyrazol-1-yl
2336	0	$(CH_2)_2C(O)CH_2$	2-fluorophenyl	cyclohexyl
2337	0	$(CH_2)_2C(O)OCH_2$	2-chlorophenyl	imidazol-1-yl
2338	0	$(CH_2)_2C(O)OCH_2$	2-bromophenyl	N,N-dimethylamido
2339	0	$(CH_2)_2C(O)OCH_2$	2-pyridyl	morpholin-1-yl

2340	0	$(CH_2)_2C(O)OCH_2$	2-pyrimidinyl	2-methylindazol-1-yl
2341	0	$(CH_2)_2C(O)OCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2342	0	$(CH_2)_2C(O)-NHCH_2$	2-chlorophenyl	pyridin-3-yl
2343	0	$(CH_2)_2C(O)-NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2344	0	$(CH_2)_2C(O)-NHCH_2$	2-pyridyl	pyrazol-1-yl
2345	0	$(CH_2)_2C(O)-NHCH_2$	2-pyrimidinyl	cyclohexyl
2346	0	$(CH_2)_2NHC(O)-NHCH_2$	2-fluorophenyl	imidazol-1-yl
2347	0	$(CH_2)_2NHC(O)-NHCH_2$	2-chlorophenyl	N,N-dimethylamido
2348	0	$(CH_2)_2NHC(O)-NHCH_2$	2-bromophenyl	morpholin-1-yl
2349	0	$(CH_2)_2NHC(O)-NHCH_2$	2-pyridyl	2-methylindazol-1-yl
2350	0	$(CH_2)_2NHC(O)-NHCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2351	0	$(CH_2)_2S(O)_2-NHCH_2$	2-chlorophenyl	pyridin-3-yl
2352	0	$(CH_2)_2S(O)_2-NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2353	0	$(CH_2)_2S(O)_2-NHCH_2$	2-pyridyl	pyrazol-1-yl
2354	0	$(CH_2)_2S(O)_2-NHCH_2$	2-pyrimidinyl	cyclohexyl

*B is substituted para to Z on A.

Table 23

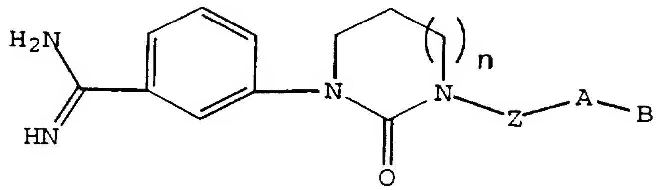


Ex.	n	Z	A*	B*
2401	1	$(CH_2)_2O$	2-fluorophenyl	imidazol-1-yl
2402	1	$(CH_2)_2O$	2-chlorophenyl	N,N-dimethylamido
2403	1	$(CH_2)_2O$	2-bromophenyl	morpholin-1-yl
2404	1	$(CH_2)_2O$	2-pyridyl	2-methylindazol-1-yl
2405	1	$(CH_2)_2O$	2-pyrimidinyl	N,N-dimethylsulfamido
2406	1	$(CH_2)_2C(O)$	2-fluorophenyl	pyridin-3-yl
2407	1	$(CH_2)_2C(O)$	2-chlorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2408	1	$(CH_2)_2C(O)$	2-bromophenyl	pyrazol-1-yl
2409	1	$(CH_2)_2C(O)$	2-pyridyl	cyclohexyl
2410	1	$(CH_2)_2C(O)O$	2-pyrimidinyl	imidazol-1-yl
2411	1	$(CH_2)_2C(O)O$	2-fluorophenyl	N,N-dimethylamido
2412	1	$(CH_2)_2C(O)O$	2-chlorophenyl	morpholin-1-yl
2413	1	$(CH_2)_2C(O)O$	2-bromophenyl	2-methylindazol-1-yl
2414	1	$(CH_2)_2C(O)NH$	2-pyridyl	N,N-dimethylsulfamido
2415	1	$(CH_2)_2C(O)NH$	2-pyrimidinyl	pyridin-3-yl
2416	1	$(CH_2)_2C(O)NH$	2-fluorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2417	1	$(CH_2)_2C(O)NH$	2-chlorophenyl	pyrazol-1-yl
2418	1	$(CH_2)_2C(O)NH$	2-bromophenyl	cyclohexyl
2419	1	$(CH_2)_2NHC(O)NH$	2-pyridyl	imidazol-1-yl
2420	1	$(CH_2)_2NHC(O)NH$	2-pyrimidinyl	N,N-dimethylamido
2421	1	$(CH_2)_2NHC(O)NH$	2-fluorophenyl	morpholin-1-yl
2422	1	$(CH_2)_2NHC(O)NH$	2-chlorophenyl	2-methylindazol-1-yl
2423	1	$(CH_2)_2S(O)_2NH$	2-bromophenyl	N,N-dimethylsulfamido
2424	1	$(CH_2)_2S(O)_2NH$	2-pyridyl	pyridin-3-yl
2425	1	$(CH_2)_2S(O)_2NH$	2-pyrimidinyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2426	1	$(CH_2)_2S(O)_2NH$	2-fluorophenyl	pyrazol-1-yl
2427	1	$(CH_2)_2S(O)_2NH$	2-chlorophenyl	cyclohexyl
2428	1	$(CH_2)_2OCH_2$	2-bromophenyl	imidazol-1-yl
2429	1	$(CH_2)_2OCH_2$	2-pyridyl	N,N-dimethylamido
2430	1	$(CH_2)_2OCH_2$	2-pyrimidinyl	morpholin-1-yl
2431	1	$(CH_2)_2OCH_2$	2-fluorophenyl	2-methylindazol-1-yl
2432	1	$(CH_2)_2OCH_2$	2-chlorophenyl	N,N-dimethylsulfamido
2433	1	$(CH_2)_2C(O)CH_2$	2-bromophenyl	pyridin-3-yl
2434	1	$(CH_2)_2C(O)CH_2$	2-pyridyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2435	1	$(CH_2)_2C(O)CH_2$	2-pyrimidinyl	pyrazol-1-yl
2436	1	$(CH_2)_2C(O)CH_2$	2-fluorophenyl	cyclohexyl
2437	1	$(CH_2)_2C(O)OCH_2$	2-chlorophenyl	imidazol-1-yl
2438	1	$(CH_2)_2C(O)OCH_2$	2-bromophenyl	N,N-dimethylamido
2439	1	$(CH_2)_2C(O)OCH_2$	2-pyridyl	morpholin-1-yl

2440	1	$(CH_2)_2C(O)OCH_2$	2-pyrimidinyl	2-methylindazol-1-yl
2441	1	$(CH_2)_2C(O)OCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2442	1	$(CH_2)_2C(O)$-$NHCH_2$	2-chlorophenyl	pyridin-3-yl
2443	1	$(CH_2)_2C(O)$-$NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2444	1	$(CH_2)_2C(O)$-$NHCH_2$	2-pyridyl	pyrazol-1-yl
2445	1	$(CH_2)_2C(O)$-$NHCH_2$	2-pyrimidinyl	cyclohexyl
2446	1	$(CH_2)_2NHC(O)$-$NHCH_2$	2-fluorophenyl	imidazol-1-yl
2447	1	$(CH_2)_2NHC(O)$-$NHCH_2$	2-chlorophenyl	N,N-dimethylamido
2448	1	$(CH_2)_2NHC(O)$-$NHCH_2$	2-bromophenyl	morpholin-1-yl
2449	1	$(CH_2)_2NHC(O)$-$NHCH_2$	2-pyridyl	2-methylindazol-1-yl
2450	1	$(CH_2)_2NHC(O)$-$NHCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2451	1	$(CH_2)_2S(O)_2$-$NHCH_2$	2-chlorophenyl	pyridin-3-yl
2452	1	$(CH_2)_2S(O)_2$-$NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2453	1	$(CH_2)_2S(O)_2$-$NHCH_2$	2-pyridyl	pyrazol-1-yl
2454	1	$(CH_2)_2S(O)_2$-$NHCH_2$	2-pyrimidinyl	cyclohexyl

*B is substituted para to Z on A.

Table 24

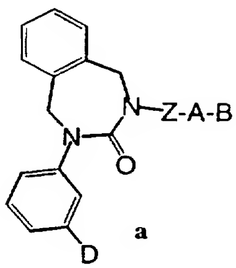


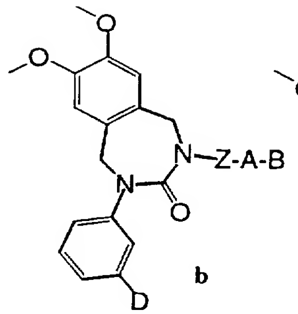
Ex.	n	Z	A*	B*
2501	2	$(CH_2)_2O$	2-fluorophenyl	imidazol-1-yl
2502	2	$(CH_2)_2O$	2-chlorophenyl	N,N-dimethylamido
2503	2	$(CH_2)_2O$	2-bromophenyl	morpholin-1-yl
2504	2	$(CH_2)_2O$	2-pyridyl	2-methylindazol-1-yl
2505	2	$(CH_2)_2O$	2-pyrimidinyl	N,N-dimethylsulfamido
2506	2	$(CH_2)_2C(O)$	2-fluorophenyl	pyridin-3-yl
2507	2	$(CH_2)_2C(O)$	2-chlorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2508	2	$(CH_2)_2C(O)$	2-bromophenyl	pyrazol-1-yl
2509	2	$(CH_2)_2C(O)$	2-pyridyl	cyclohexyl
2510	2	$(CH_2)_2C(O)O$	2-pyrimidinyl	imidazol-1-yl
2511	2	$(CH_2)_2C(O)O$	2-fluorophenyl	N,N-dimethylamido
2512	2	$(CH_2)_2C(O)O$	2-chlorophenyl	morpholin-1-yl
2513	2	$(CH_2)_2C(O)O$	2-bromophenyl	2-methylindazol-1-yl
2514	2	$(CH_2)_2C(O)NH$	2-pyridyl	N,N-dimethylsulfamido
2515	2	$(CH_2)_2C(O)NH$	2-pyrimidinyl	pyridin-3-yl
2516	2	$(CH_2)_2C(O)NH$	2-fluorophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2517	2	$(CH_2)_2C(O)NH$	2-chlorophenyl	pyrazol-1-yl
2518	2	$(CH_2)_2C(O)NH$	2-bromophenyl	cyclohexyl
2519	2	$(CH_2)_2NHC(O)NH$	2-pyridyl	imidazol-1-yl
2520	2	$(CH_2)_2NHC(O)NH$	2-pyrimidinyl	N,N-dimethylamido
2521	2	$(CH_2)_2NHC(O)NH$	2-fluorophenyl	morpholin-1-yl
2522	2	$(CH_2)_2NHC(O)NH$	2-chlorophenyl	2-methylindazol-1-yl
2523	2	$(CH_2)_2S(O)_2NH$	2-bromophenyl	N,N-dimethylsulfamido
2524	2	$(CH_2)_2S(O)_2NH$	2-pyridyl	pyridin-3-yl
2525	2	$(CH_2)_2S(O)_2NH$	2-pyrimidinyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2526	2	$(CH_2)_2S(O)_2NH$	2-fluorophenyl	pyrazol-1-yl
2527	2	$(CH_2)_2S(O)_2NH$	2-chlorophenyl	cyclohexyl
2528	2	$(CH_2)_2OCH_2$	2-bromophenyl	imidazol-1-yl
2529	2	$(CH_2)_2OCH_2$	2-pyridyl	N,N-dimethylamido
2530	2	$(CH_2)_2OCH_2$	2-pyrimidinyl	morpholin-1-yl
2531	2	$(CH_2)_2OCH_2$	2-fluorophenyl	2-methylindazol-1-yl
2532	2	$(CH_2)_2OCH_2$	2-chlorophenyl	N,N-dimethylsulfamido
2533	2	$(CH_2)_2C(O)CH_2$	2-bromophenyl	pyridin-3-yl
2534	2	$(CH_2)_2C(O)CH_2$	2-pyridyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2535	2	$(CH_2)_2C(O)CH_2$	2-pyrimidinyl	pyrazol-1-yl
2536	2	$(CH_2)_2C(O)CH_2$	2-fluorophenyl	cyclohexyl
2537	2	$(CH_2)_2C(O)OCH_2$	2-chlorophenyl	imidazol-1-yl
2538	2	$(CH_2)_2C(O)OCH_2$	2-bromophenyl	N,N-dimethylamido
2539	2	$(CH_2)_2C(O)OCH_2$	2-pyridyl	morpholin-1-yl

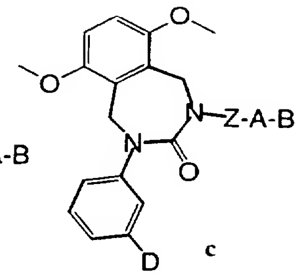
2540	2	$(CH_2)_2C(O)OCH_2$	2-pyrimidinyl	2-methylindazol-1-yl
2541	2	$(CH_2)_2C(O)OCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2542	2	$(CH_2)_2C(O)-NHCH_2$	2-chlorophenyl	pyridin-3-yl
2543	2	$(CH_2)_2C(O)-NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2544	2	$(CH_2)_2C(O)-NHCH_2$	2-pyridyl	pyrazol-1-yl
2545	2	$(CH_2)_2C(O)-NHCH_2$	2-pyrimidinyl	cyclohexyl
2546	2	$(CH_2)_2NHC(O)-NHCH_2$	2-fluorophenyl	imidazol-1-yl
2547	2	$(CH_2)_2NHC(O)-NHCH_2$	2-chlorophenyl	N,N-dimethylamido
2548	2	$(CH_2)_2NHC(O)-NHCH_2$	2-bromophenyl	morpholin-1-yl
2549	2	$(CH_2)_2NHC(O)-NHCH_2$	2-pyridyl	2-methylindazol-1-yl
2550	2	$(CH_2)_2NHC(O)-NHCH_2$	2-fluorophenyl	N,N-dimethylsulfamido
2551	2	$(CH_2)_2S(O)_2-NHCH_2$	2-chlorophenyl	pyridin-3-yl
2552	2	$(CH_2)_2S(O)_2-NHCH_2$	2-bromophenyl	2-((5'-trifluormethyl) tetrazol-1'-yl)phenyl
2553	2	$(CH_2)_2S(O)_2-NHCH_2$	2-pyridyl	pyrazol-1-yl
2554	2	$(CH_2)_2S(O)_2-NHCH_2$	2-pyrimidinyl	cyclohexyl

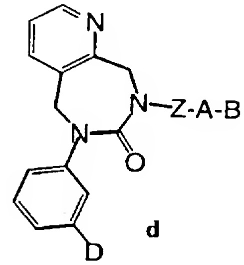
*B is substituted para to Z on A.

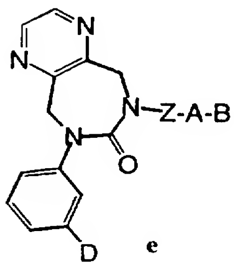
Table 25*

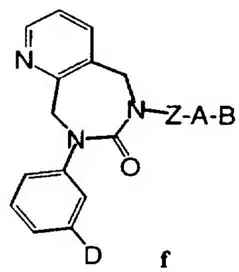

a

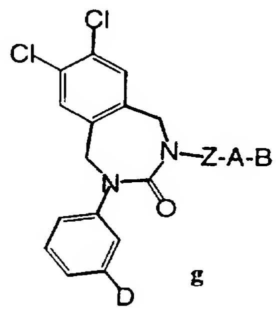

b

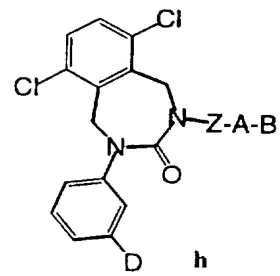

c

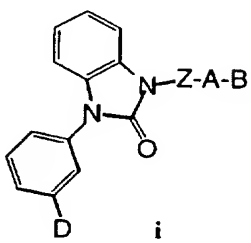

d

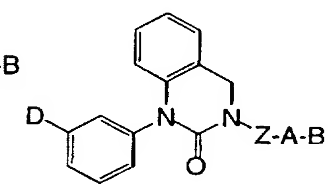

e

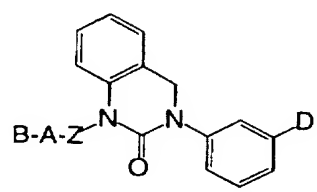

f

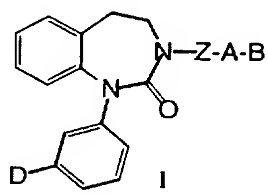

g

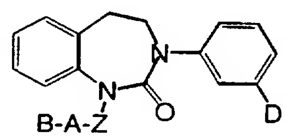

h


i


j


k


l


m

Ex.	D	Z	A^1	A^2	B
2601	$C(=NH)NH_2$	bond	CH	CH	amino
2602	$C(=NH)NH_2$	bond	CH	CH	amidino
2603	$C(=NH)NH_2$	bond	CH	CH	guanidino
2604	$C(=NH)NH_2$	bond	CH	CH	2-sulfamidophenyl
2605	$C(=NH)NH_2$	bond	CH	CH	2-trifluoromethylphenyl
2606	$C(=NH)NH_2$	CH_2	CH	CH	amino
2607	$C(=NH)NH_2$	CH_2	CH	CH	amidino
2608	$C(=NH)NH_2$	CH_2	CH	CH	guanidino
2609	$C(=NH)NH_2$	CH_2	CH	CH	2-sulfamidophenyl
2610	$C(=NH)NH_2$	CH_2	CH	CH	2-trifluoromethylphenyl
2611	$C(=NH)NH_2$	bond	N	CH	amino
2612	$C(=NH)NH_2$	bond	N	CH	amidino
2613	$C(=NH)NH_2$	bond	N	CH	guanidino
2614	$C(=NH)NH_2$	bond	N	CH	2-sulfamidophenyl
2615	$C(=NH)NH_2$	bond	N	CH	2-trifluoromethylphenyl
2616	$C(=NH)NH_2$	CH_2	N	CH	amino

2617	C(=NH)NH_2	CH_2	N	CH	amidino
2618	C(=NH)NH_2	CH_2	N	CH	guanidino
2619	C(=NH)NH_2	CH_2	N	CH	2-sulfamidophenyl
2620	C(=NH)NH_2	CH_2	N	CH	2-trifluoromethylphenyl
2621	C(=NH)NH_2	bond	N	N	amino
2622	C(=NH)NH_2	bond	N	N	amidino
2623	C(=NH)NH_2	bond	N	N	guanidino
2624	C(=NH)NH_2	bond	N	N	2-sulfamidophenyl
2625	C(=NH)NH_2	bond	N	N	2-trifluoromethylphenyl
2626	C(=NH)NH_2	CH_2	N	N	amino
2627	C(=NH)NH_2	CH_2	N	N	amidino
2628	C(=NH)NH_2	CH_2	N	N	guanidino
2629	C(=NH)NH_2	CH_2	N	N	2-sulfamidophenyl
2630	C(=NH)NH_2	CH_2	N	N	2-trifluoromethylphenyl
2631	C(=NH)NH_2	bond	CH	CH	imidazol-1-yl
2632	C(=NH)NH_2	bond	CH	CH	morpholin-1-yl
2633	C(=NH)NH_2	bond	CH	CH	2-methylimidazol-1-yl
2634	C(=NH)NH_2	bond	CH	CH	pyridin-3-yl
2635	C(=NH)NH_2	bond	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2636	C(=NH)NH_2	bond	CH	CH	pyrazol-1-yl
2637	C(=NH)NH_2	bond	CH	CH	phenyl
2638	C(=NH)NH_2	bond	CH	CH	cyclohexyl
2639	C(=NH)NH_2	bond	CH	CH	N,N-dimethylsulfamido
2640	C(=NH)NH_2	bond	CH	CH	N,N-dimethylamido
2641	C(=NH)NH_2	bond	N	CH	imidazol-1-yl
2642	C(=NH)NH_2	bond	N	CH	morpholin-1-yl
2643	C(=NH)NH_2	bond	N	CH	2-methylimidazol-1-yl
2644	C(=NH)NH_2	bond	N	CH	pyridin-3-yl
2645	C(=NH)NH_2	bond	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2646	C(=NH)NH_2	bond	N	CH	pyrazol-1-yl
2647	C(=NH)NH_2	bond	N	CH	phenyl
2648	C(=NH)NH_2	bond	N	CH	cyclohexyl
2649	C(=NH)NH_2	bond	N	CH	N,N-dimethylsulfamido
2650	C(=NH)NH_2	bond	N	CH	N,N-dimethylamido
2651	C(=NH)NH_2	bond	N	N	imidazol-1-yl
2652	C(=NH)NH_2	bond	N	N	morpholin-1-yl
2653	C(=NH)NH_2	bond	N	N	2-methylimidazol-1-yl
2654	C(=NH)NH_2	bond	N	N	pyridin-3-yl
2655	C(=NH)NH_2	bond	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
2656	C(=NH)NH_2	bond	N	N	pyrazol-1-yl
2657	C(=NH)NH_2	bond	N	N	phenyl
2658	C(=NH)NH_2	bond	N	N	cyclohexyl
2659	C(=NH)NH_2	bond	N	N	N,N-dimethylsulfamido
2660	C(=NH)NH_2	bond	N	N	N,N-dimethylamido
2661	C(=NH)NH_2	bond	F	CH	imidazol-1-yl
2662	C(=NH)NH_2	bond	F	CH	morpholin-1-yl
2663	C(=NH)NH_2	bond	F	CH	2-methylimidazol-1-yl
2664	C(=NH)NH_2	bond	F	CH	pyridin-3-yl
2665	C(=NH)NH_2	bond	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl

2666	C(=NH)NH$_2$	bond	F	CH	pyrazol-1-yl
2667	C(=NH)NH$_2$	bond	F	CH	phenyl
2668	C(=NH)NH$_2$	bond	F	CH	cyclohexyl
2669	C(=NH)NH$_2$	bond	F	CH	N,N-dimethylsulfamido
2670	C(=NH)NH$_2$	bond	F	CH	N,N-dimethylamido
2671	C(=NH)NH$_2$	bond	Cl	CH	imidazol-1-yl
2672	C(=NH)NH$_2$	bond	Cl	CH	morpholin-1-yl
2673	C(=NH)NH$_2$	bond	Cl	CH	2-methylimidazol-1-yl
2674	C(=NH)NH$_2$	bond	Cl	CH	pyridin-3-yl
2675	C(=NH)NH$_2$	bond	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2676	C(=NH)NH$_2$	bond	Cl	CH	pyrazol-1-yl
2677	C(=NH)NH$_2$	bond	Cl	CH	phenyl
2678	C(=NH)NH$_2$	bond	Cl	CH	cyclohexyl
2679	C(=NH)NH$_2$	bond	Cl	CH	N,N-dimethylsulfamido
2680	C(=NH)NH$_2$	bond	Cl	CH	N,N-dimethylamido
2681	C(=NH)NH$_2$	bond	Br	CH	imidazol-1-yl
2682	C(=NH)NH$_2$	bond	Br	CH	morpholin-1-yl
2683	C(=NH)NH$_2$	bond	Br	CH	2-methylimidazol-1-yl
2684	C(=NH)NH$_2$	bond	Br	CH	pyridin-3-yl
2685	C(=NH)NH$_2$	bond	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2686	C(=NH)NH$_2$	bond	Br	CH	pyrazol-1-yl
2687	C(=NH)NH$_2$	bond	Br	CH	phenyl
2688	C(=NH)NH$_2$	bond	Br	CH	cyclohexyl
2689	C(=NH)NH$_2$	bond	Br	CH	N,N-dimethylsulfamido
2690	C(=NH)NH$_2$	bond	Br	CH	N,N-dimethylamido
2691	C(=NH)NH$_2$	CH$_2$	CH	CH	imidazol-1-yl
2692	C(=NH)NH$_2$	CH$_2$	CH	CH	morpholin-1-yl
2693	C(=NH)NH$_2$	CH$_2$	CH	CH	2-methylimidazol-1-yl
2694	C(=NH)NH$_2$	CH$_2$	CH	CH	pyridin-3-yl
2695	C(=NH)NH$_2$	CH$_2$	CH	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2696	C(=NH)NH$_2$	CH$_2$	CH	CH	pyrazol-1-yl
2697	C(=NH)NH$_2$	CH$_2$	CH	CH	phenyl
2698	C(=NH)NH$_2$	CH$_2$	CH	CH	cyclohexyl
2699	C(=NH)NH$_2$	CH$_2$	CH	CH	N,N-dimethylsulfamido
2700	C(=NH)NH$_2$	CH$_2$	CH	CH	N,N-dimethylamido
2701	C(=NH)NH$_2$	CH$_2$	N	CH	imidazol-1-yl
2702	C(=NH)NH$_2$	CH$_2$	N	CH	morpholin-1-yl
2703	C(=NH)NH$_2$	CH$_2$	N	CH	2-methylimidazol-1-yl
2704	C(=NH)NH$_2$	CH$_2$	N	CH	pyridin-3-yl
2705	C(=NH)NH$_2$	CH$_2$	N	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2706	C(=NH)NH$_2$	CH$_2$	N	CH	pyrazol-1-yl
2707	C(=NH)NH$_2$	CH$_2$	N	CH	phenyl
2708	C(=NH)NH$_2$	CH$_2$	N	CH	cyclohexyl
2709	C(=NH)NH$_2$	CH$_2$	N	CH	N,N-dimethylsulfamido
2710	C(=NH)NH$_2$	CH$_2$	N	CH	N,N-dimethylamido
2711	C(=NH)NH$_2$	CH$_2$	N	N	imidazol-1-yl
2712	C(=NH)NH$_2$	CH$_2$	N	N	morpholin-1-yl
2713	C(=NH)NH$_2$	CH$_2$	N	N	2-methylimidazol-1-yl
2714	C(=NH)NH$_2$	CH$_2$	N	N	pyridin-3-yl

2715	C(=NH)NH$_2$	CH$_2$	N	N	2-(5'-trifluoromethyl) tetrazol-1'-yl
2716	C(=NH)NH$_2$	CH$_2$	N	N	pyrazol-1-yl
2717	C(=NH)NH$_2$	CH$_2$	N	N	phenyl
2718	C(=NH)NH$_2$	CH$_2$	N	N	cyclohexyl
2719	C(=NH)NH$_2$	CH$_2$	N	N	N,N-dimethylsulfamido
2720	C(=NH)NH$_2$	CH$_2$	N	N	N,N-dimethylamido
2721	C(=NH)NH$_2$	CH$_2$	F	CH	imidazol-1-yl
2722	C(=NH)NH$_2$	CH$_2$	F	CH	morpholin-1-yl
2723	C(=NH)NH$_2$	CH$_2$	F	CH	2-methylimidazol-1-yl
2724	C(=NH)NH$_2$	CH$_2$	F	CH	pyridin-3-yl
2725	C(=NH)NH$_2$	CH$_2$	F	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2726	C(=NH)NH$_2$	CH$_2$	F	CH	pyrazol-1-yl
2727	C(=NH)NH$_2$	CH$_2$	F	CH	phenyl
2728	C(=NH)NH$_2$	CH$_2$	F	CH	cyclohexyl
2729	C(=NH)NH$_2$	CH$_2$	F	CH	N,N-dimethylsulfamido
2730	C(=NH)NH$_2$	CH$_2$	F	CH	N,N-dimethylamido
2731	C(=NH)NH$_2$	CH$_2$	Cl	CH	imidazol-1-yl
2732	C(=NH)NH$_2$	CH$_2$	Cl	CH	morpholin-1-yl
2733	C(=NH)NH$_2$	CH$_2$	Cl	CH	2-methylimidazol-1-yl
2734	C(=NH)NH$_2$	CH$_2$	Cl	CH	pyridin-3-yl
2735	C(=NH)NH$_2$	CH$_2$	Cl	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2736	C(=NH)NH$_2$	CH$_2$	Cl	CH	pyrazol-1-yl
2737	C(=NH)NH$_2$	CH$_2$	Cl	CH	phenyl
2738	C(=NH)NH$_2$	CH$_2$	Cl	CH	cyclohexyl
2739	C(=NH)NH$_2$	CH$_2$	Cl	CH	N,N-dimethylsulfamido
2740	C(=NH)NH$_2$	CH$_2$	Cl	CH	N,N-dimethylamido
2741	C(=NH)NH$_2$	CH$_2$	Br	CH	imidazol-1-yl
2742	C(=NH)NH$_2$	CH$_2$	Br	CH	morpholin-1-yl
2743	C(=NH)NH$_2$	CH$_2$	Br	CH	2-methylimidazol-1-yl
2744	C(=NH)NH$_2$	CH$_2$	Br	CH	pyridin-3-yl
2745	C(=NH)NH$_2$	CH$_2$	Br	CH	2-(5'-trifluoromethyl) tetrazol-1'-yl
2746	C(=NH)NH$_2$	CH$_2$	Br	CH	pyrazol-1-yl
2747	C(=NH)NH$_2$	CH$_2$	Br	CH	phenyl
2748	C(=NH)NH$_2$	CH$_2$	Br	CH	cyclohexyl
2749	C(=NH)NH$_2$	CH$_2$	Br	CH	N,N-dimethylsulfamido
2750	C(=NH)NH$_2$	CH$_2$	Br	CH	N,N-dimethylamido

*Each entry in Table 25 is intended to correspond individually to each of formulae a-m.

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms.

The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa. The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o - v_s)/v_s = I/(K_i\ (1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Using the methodology described above, a number of compounds of the present invention were found to exhibit a K_i of ≤ 1 µm, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of the compounds of the present invention can be demonstrated in a rat vena cava thrombosis model. In this model Male Sprague-Dawley rats weighing 350-450 grams anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (110 mg/kg i.m.) are used. A carotid artery, a jugular vein and a femoral vein are cannulated for blood sampling, drug infusion and hypotonic saline injection, respectively. The abdominal vena cava is isolated and all its side-branches are ligated beneath the left renal vein. Thrombus formation is induced by rapid injection of 1 ml hypotonic saline (0.225%) into the vena cava. This is followed 15 seconds later by a 15-minute stasis of an isolated segment (about 1 cm) of the vena cava. The formed thrombus in the vena cava is removed and immediately weighed.

Test compounds or vehicle are given as continuous intravenous infusions or orally starting 1 hour before the injection of hypotonic saline. Arterial blood samples (1.5 ml) for the determination of clotting times are collected before and 1 hour after the infusion or oral dosing of test compounds or vehicle. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) are also considered to be useful as inhibitors of serine proteases, notably human

thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 5 μm, thereby confirming the utility of the compounds of the invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A2-receptor

antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator

complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but no compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin

patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if

necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

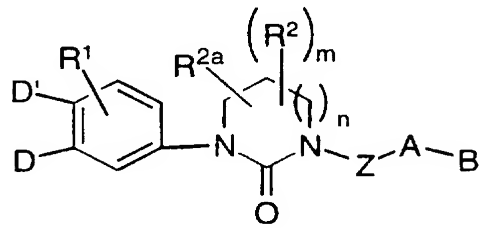
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the

scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY LETTER PATENT OF UNITED STATES IS:

1. A compound of formula I:



I

or stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

one of D and D′ is selected from CN, $C(=NR^{11})NR^{12}R^{13}$, $NHC(=NR^{11})NR^{12}R^{13}$, $NR^{12}CH(=NR^{11})$, $C(O)NR^{12}R^{13}$, and $(CH_2)_tNR^{12}R^{13}$ and the other is H;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, C_{1-4} alkyl, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNR^4SO_2R^5$;

R^2 is selected from H, =O, C_{1-4} alkyl substituted with 0, 1, or 2 R^7, C_{2-6} alkenyl substituted with 0, 1, or 2 R^7, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, C_{3-10} carbocyclic residue substituted with 0-2 R^6; and, 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^{2a} is absent;

alternatively, R^2 and R^{2a} may be present on adjacent carbon atoms and combine to form a benzene ring substituted with 0-2 R^{10} or a 5-6 membered aromatic heterocycle containing 0-2 heteratoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{10a};

R^3 and $R^{3'}$ are independently selected from H, C_{1-4} alkyl, benzyl and phenyl;

R^3 and $R^{3'}$ may be taken together to form a 5 or 6 membered ring substituted with 0-2 R^6;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, phenyl and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl, phenyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_2NR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_2OC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)O(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^6, and

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

B is selected from:

X-Y, $NR^3R^{3'}$, $C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$,

benzyl substituted with 0-2 R^6,

C_{3-10} carbocyclic residue substituted with 0-2 R^6, and

5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-C(O)O-$, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, $-OC(O)-$, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$,

$-S(O)_pCR^3R^{3\prime}-$, $-CR^3R^{3\prime}S(O)_p-$, $-S(O)_2NR^3-$, $-NR^3S(O)_2-$, $-NR^3S(O)_2CR^3R^{3\prime}-$, $-CR^3R^{3\prime}S(O)_2NR^3-$, $-NR^3S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-C(O)NR^3CR^3R^{3\prime}-$, $-NR^3C(O)CR^3R^{3\prime}-$, $-CR^3R^{3\prime}C(O)NR^3-$, $-CR^3R^{3\prime}NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3\prime}-$, $-CR^3R^{3\prime}NR^3-$, O, $-CR^3R^{3\prime}O-$, $-OCR^3R^{3\prime}-$, S, $-CR^3R^{3\prime}S-$, and $-SCR^3R^{3\prime}-$;

Y is selected from:
C_{1-4} alkyl substituted with 0-2 R^6
C_{3-10} carbocyclic residue substituted with 0-2 R^6, and
5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, NR^3SO_2-C_{1-4} alkyl, SO_2-phenyl, and $NR^3SO_2R^8$;

R^7 is selected from:
C_{3-10} carbocyclic residue substituted with 0-2 R^6; and,
5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^8 is selected from:
C_{3-10} carbocyclic residue substituted with 0-2 R^9; and,
5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^9;

R^9 is selected from H, OH, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, and NR^3SO_2-C_{1-4} alkyl;

R^{10} is selected from H, OR^3, halo, C_{1-4} alkyl, CN, NO_2, $NR^3R^{3\prime}$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)OR^{3\prime}$, NR^3SO_2-phenyl, and NR^3SO_2-C_{1-4} alkyl;

R^{10a} if a substituent on nitrogen is selected from H and C_{1-4} alkyl;

R^{10a} if a substituent on carbon is selected from H, C_{1-4} alkyl, $NR^3R^{3'}$, $NR^3C(O)R^{3'}$, $NR^3C(O)OR^{3'}$, NR^3SO_2-phenyl, and NR^3SO_2-C_{1-4} alkyl;

R^{11} is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^{12} is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

R^{13} is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

n is selected from 0, 1, 2, and 3;

m is selected from 0 and 1;

p is selected from 0, 1, and 2;

q is selected from 1, 2, 3, 4, and 5; and,

r is selected from 0, 1, and 2.

2. A compound according to Claim 1, wherein:

D is $C(=NH)NH_2$;

D' is H;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNHSO_2R^5$;

R^2 is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, C_{3-10} carbocyclic residue substituted with 0-2 R^6; and, 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^6;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$; and,

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-C(O)O-$, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, $-OC(O)-$, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-CR^3R^{3'}S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3'}-$, $-CR^3R^{3'}NR^3-$, O, $-CR^3R^{3'}O-$, and $-OCR^3R^{3'}-$.

3. A compound according to Claim 2, wherein:

R^1 is selected from H, OR^3, $(CH_2)OR^3$, halo, $NR^4R^{4'}$, $(CH_2)NR^4R^{4'}$, $C(=O)R^4$, $(CH_2)C(=O)R^4$, $NHC(=O)R^4$, $(CH_2)NHC(=O)R^4$, SO_2R^5, $(CH_2)SO_2R^5$, $NHSO_2R^5$, and $(CH_2)NHSO_2R^5$;

R^2 is selected from H, =O, OR^3, $C(O)R^4$, $(CH_2)C(O)R^4$, $OC(O)R^4$, $NR^4R^{4'}$, $NR^3C(O)R^4$, and $NR^4SO_2R^5$;

A is selected from:

C_{5-6} carbocyclic residue substituted with 0-1 R^6, and

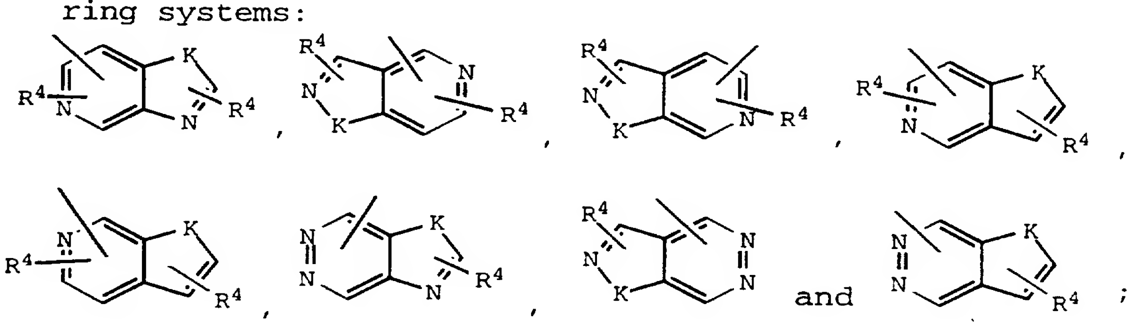
5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N and O substituted with 0-1 R^6;

B is selected from: Y, X-Y, and NR^2R^{2a};

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, isoindazole, and benzothiadiazole;

Y may also be selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N;

X is selected from $-CH_2-$, $-C(O)-$, $-C(O)CHR^3-$, $-CHR^3C(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3\prime}-$, $-CHR^3S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3-$, $-NR^3CHR^3-$, and $-CHR^3NR^3$;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $SO_2NR^3R^{3\prime}$, SO_2-phenyl, NR^3SO_2-C_{1-4} alkyl, and $NR^3SO_2R^8$;

R^8 is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^9; and,

5-6 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^9;

R^9 is selected from H, OH, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $NR^3C(O)NR^3R^{3\prime}$, $SO_2NR^3R^{3\prime}$, $NR^3SO_2NR^3R^{3\prime}$, and NR^3SO_2-C_{1-4} alkyl; and,

p is 2.

4. A compound according to Claim 3, wherein:

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, and $(CH_2)_rS(CH_2)_r$;

X is selected from $-CH_2-$, $-C(O)-$, $-C(O)CHR^3-$, $-CHR^3C(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3\prime}-$, $-CHR^3S(O)_p-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, and $-NR^3C(O)-$;

R^6 is selected from H, OH, CF_3, $(CH_2)_nOR^3$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^3R^{3\prime}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3\prime}$, $SO_2NR^3R^{3\prime}$, SO_2-phenyl, and NR^3SO_2-C_{1-4} alkyl;

m is 1; and,

r is selected from 0 and 1.

5. A compound according to Claim 4, wherein:

R^3 and $R^{3'}$ are independently selected from H and C_{1-4} alkyl;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, and $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$;

A is selected from phenyl substituted with 0-1 R^6 and a 6 membered heterocyclic system containing 1 N and 0-1 O atoms and substituted with 0-1 R^6;

X is selected from $-CH_2-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-S(O)_2NR^3-$, $-C(O)NR^3-$, and ;

Y is selected from phenyl, i-propyl, quinolynyl, thiadizolyl, benzothiadiazolyl, thiophenyl, pyridyl, cyclohexyl, and naphthyl, each of which is substituted with 0-2 R^6; and,

n is selected from 0, 1, and 2.

6. A compound according to Claim 5, wherein:

R^3 and $R^{3'}$ are independently selected from H and methyl;

Z is selected from a bond, CH_2, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-$;

A is selected from phenyl substituted with 0-1 R^6, and piperidinyl substituted with 0-1 R^6; and,

n is 2.

7. A compound according to Claim 6, wherein the compound is selected from:

N-(3-amidinophenyl)-N'-((4-((2-sulphonamido)phenyl)phenyl)-methyl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-2-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-3-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-4-yl)piperidin-4-yl) cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(a-phenethyl)piperidin-4-yl)cyclo-heptylurea;

N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperi-din-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(phenyl)sulfonylpiperidin-4-yl)-cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(quinolin-8-yl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-fluorophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-acetamidophenyl)sulfonyl-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(3-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-acetamido-phenyl)methane)-sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((thiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-chlorothiophen-2-yl)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-carbomethoxythiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((benzo-2,1,3-thiadiazo-4-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((cyclohexyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((isopropyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((phenyl)sulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((isopropyl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-amino-4-methylthiazol-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-acetamido-4-methylthiazol-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(6-carbomethoxyphenyl-sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(3-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-pyridylmethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(phenyl-N''-methylsulfamido)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((4-phenylsulfonylthiophen-2-yl)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-pyridylmethylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(thiophen-2-ylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-fluorobenzylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-pyridylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-trifluormethyl-phenylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(2-phenylisopropylsulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((1-((phenyl)-1,1-dimethyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)carbamide)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((thiophen-2-yl)sulfonyl)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-(methyl((phenyl-methane)sulfonyl)morpholin-3-yl))cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-benzyl)piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-(benzyl)sulfonyl)-piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-((N-(thiophen-2-yl)sulfonyl)piperidin-3-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(4-(2-sulfonamido-phenyl)phenyl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(5-(2-sulfonamido-phenyl)pyridin-2-yl)cycloheptylurea; and,

N-(3-amidinophenyl)-N'-(methyl(4-(2-sulfonamidophenyl)phenyl))cycloheptylurea;

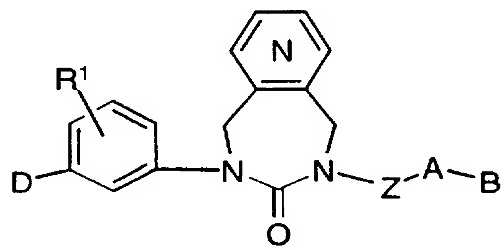
or stereoisomers or pharmaceutically acceptable salt forms thereof.

8. A compound according to Claim 1, wherein:

n is 2; and,

R^2 and R^{2a} are on adjacent carbon atoms and combine to form a benzene ring substituted with 0-2 R^{10} or a 5-6 membered aromatic heterocycle containing 0-2 heteratoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{10a}.

9. A compound according to Claim 8, wherein the compound is of formula II:



II

wherein;

ring N contains 0-2 N atoms and is substituted with 0-2 R^{10}; and,

D is selected from CN, $C(=NR^{11})NR^{12}R^{13}$, $NHC(=NR^{11})NR^{12}R^{13}$, $NR^{12}CH(=NR^{11})$, $C(O)NR^{12}R^{13}$, and $(CH_2)_tNR^{12}R^{13}$.

10. A compound according to Claim 9, wherein:

D is $C(=NH)NH_2$;

R^1 is selected from H, $(CH_2)_rOR^3$, halo, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNHSO_2R^5$;

R^4 and $R^{4'}$ are independently selected from H, OR^3, C_{1-4} alkyl, and $NR^3R^{3'}$;

R^5 is selected from C_{1-4} alkyl and $NR^3R^{3'}$;

Z is selected from a bond, C_{1-4} alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, and $(CH_2)_rSO_2NR^3(CH_2)_r$; and,

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-C(O)O-$, $-C(O)OCR^3R^{3'}-$, $-CR^3R^{3'}C(O)O-$, $-OC(O)-$, $-OC(O)CR^3R^{3'}-$, $-CR^3R^{3'}OC(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-CR^3R^{3'}S(O)_p-$, $-C(O)NR^3-$, $-NR^3C(O)-$, $-NR^3C(O)O-$, $-OC(O)NR^3-$, $-NR^3C(O)NR^3-$, $-NR^3-$, $-NR^3CR^3R^{3'}-$, $-CR^3R^{3'}NR^3-$, O, $-CR^3R^{3'}O-$, and $-OCR^3R^{3'}-$.

11. A compound according to Claim 10, wherein:

Z is selected from a bond, C_{1-4} alkylene, $C(O)NR^3(CH_2)_r$, $S(O)_2$, $S(O)_2CH_2$, and $(CH_2)_rSO_2NR^3(CH_2)_r$;

A is selected from phenyl substituted with 0-1 R^6 and 6 membered heterocyclic system containing 1 N and substituted with 0-1 R^6; and,

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(O)CR^3R^{3'}-$, $-CR^3R^{3'}C(O)-$, $-S(O)_p-$, $-S(O)_pCR^3R^{3'}-$, $-C(O)NR^3-$, and, $-NR^3-$

12. A compound according to Claim 11, wherein the compound is selected from:

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one;

1,2,4,5-tetrahydro-2-(thiopen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-3H-2,4-benzodiazepin-3-one;

1,2,4,5-tetrahydro-2-((phenyl)methane)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one; and,

1,2,4,5-tetrahydro-2-(thiophen-2-yl)-sulfonyl)piperidin-4-yl)-4-(3-amidinophenyl)-7,8-dimethoxy-3H-2,4-benzodiazepin-3-one.

13. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 3 or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 9 or a pharmaceutically acceptable salt thereof.

17. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

18. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 2 or a pharmaceutically acceptable salt thereof.

19. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 3 or a pharmaceutically acceptable salt thereof.

20. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 9 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/06431

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D243/04 C07D401/04 C07D401/14 C07D417/14 C07D409/14
C07D413/04 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 96 36639 A (SEARLE & CO.) 21 November 1996 cited in the application see the whole document ---	1-20
X	WO 94 19329 A (DU PONT MERCK) 1 September 1994 cited in the application see claim 1 ---	1-16
X	EP 0 587 134 A (THOMAE GMBH) 16 March 1994 cited in the application see claim 1 ---	1-20
A	WO 95 06038 A (SEARLE & CO.) 2 March 1995 cited in the application see the whole document ---	1-20
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 1997	04.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kissler, B

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 96 38421 A (BERLEX LAB. INC.) 5 December 1996 cited in the application see the whole document ---	1-20
A	EP 0 503 548 A (THOMAE) 16 September 1992 see the whole document -----	1-20

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/06431

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 17-20
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ **As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.**

2. ☐ **As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.**

3. ☐ **As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:**

4. ☐ **No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/06431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9636639 A	21-11-96	AU 5735996 A	29-11-96
WO 9419329 A	01-09-94	US 5610294 A	11-03-97
		AU 3289595 A	23-05-96
		AU 6549394 A	14-09-94
		CA 2156594 A	01-09-94
		EP 0686151 A	13-12-95
		JP 8509700 T	15-10-96
		US 5506355 A	09-04-96
		ZA 9401325 A	25-08-95
		US 5559252 A	24-09-96
EP 587134 A	16-03-94	DE 4230470 A	14-04-94
		DE 4302052 A	28-07-94
		DE 4309213 A	29-09-94
		AU 4624993 A	24-03-94
		BG 98103 A	15-07-94
		CA 2105934 A	12-03-94
		CN 1092769 A	28-09-94
		CZ 9301881 A	16-11-94
		FI 933942 A	12-03-94
		HU 71496 A	28-11-95
		JP 6263740 A	20-09-94
		NO 933248 A	14-03-94
		NZ 248633 A	28-08-95
		PL 300347 A	16-05-94
		SK 94393 A	10-08-94
		ZA 9306689 A	10-03-95
WO 9506038 A	02-03-95	US 5430043 A	04-07-95
		AU 7401994 A	21-03-95
		CA 2168345 A	02-03-95
		EP 0715623 A	12-06-96
		JP 9501692 T	18-02-97
		US 5489594 A	06-02-96
		ZA 9405836 A	04-08-95
WO 9638421 A	05-12-96	US 5612363 A	18-03-97
		AU 5974696 A	18-12-96

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/06431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 503548 A	16-09-92	DE 4107857 A	17-09-92
		AT 154013 T	15-06-97
		AU 654340 B	03-11-94
		AU 1280392 A	17-09-92
		CA 2062655 A	13-09-92
		DE 59208559 D	10-07-97
		IL 101203 A	31-12-95
		JP 4368372 A	21-12-92
		NZ 241928 A	27-06-94
		SK 74592 A	08-12-93
		US 5478942 A	26-12-95
		US 5276049 A	04-01-94
		ZA 9201804 A	13-09-93

Form PCT/ISA/210 (patent family annex) (July 1992)